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L5	L4 and l3	17	L5
L4	l1 with mutat$	17	L4
L3	LQT syndrome or long QT syndrome	133	L3
L2	L1 or human ether a-go-go related gene	81	L2
L1	HERG	81	L1

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=> s herg or human ether a-go-go gene
L1 1331 HERG OR HUMAN ETHER A-GO-GO GENE

=> s long QT or lQT
L2 4523 LONG QT OR LQT

=> s l1 and l2
L3 569 L1 AND L2

=> s l1 (3a) mutat?
L4 281 L1 (3A) MUTAT?

=> s l4 and l2
L5 244 L4 AND L2

=> s l5 and (drug screen? or agent? or pharmac?)
L6 36 L5 AND (DRUG SCREEN? OR AGENT? OR PHARMAC?)

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L7 22 DUP REM L6 (14 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:214853 BIOSIS
DN PREV200200214853
TI The binding site for channel blockers that rescue misprocessed human ***long*** ***QT*** syndrome type 2 ether-a-gogo-related gene (***HERG***) ***mutations*** .
AU Ficker, Eckhard (1); Obejero-Paz, Carlos A.; Zhao, Shuxia; Brown, Arthur M.
CS (1) Rammelkamp Center, MetroHealth Medical Center, 2500 MetroHealth Dr., Cleveland, OH, 44109: eficker@metrohealth.org USA
SO Journal of Biological Chemistry, (February 15, 2002) Vol. 277, No. 7, pp. 4989-4998. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Mutations in the human ether-a-gogo-related gene (HERG) K+ channel gene cause chromosome 7-linked ***long*** ***QT*** syndrome type 2 (LQT2), which is characterized by a prolonged QT interval in the electrocardiogram and an increased susceptibility to life-threatening cardiac arrhythmias. LQT2 mutations produce loss-of-function phenotypes and reduce IKr currents either by the heteromeric assembly of non- or malfunctioning channel subunits with wild type subunits at the cell surface or by retention of misprocessed mutant HERG channels in the endoplasmic reticulum. Misprocessed mutations often encode for channel proteins that are functional upon incorporation into the plasma membrane. As a result the ***pharmacological*** correction of folding defects and restoration of protein function are of considerable interest. Here we report that the trafficking-deficient pore ***mutation*** ***HERG*** G601S was rescued by a series of HERG channel blockers that increased cell surface expression. Rescue by these ***pharmacological*** chaperones varied directly with their blocking potency. We used structure-activity relationships and site-directed mutagenesis to define the binding site of the ***pharmacological*** chaperones. We found that binding occurred in the inner cavity and correlated with hydrophobicity and cationic charge. Rescue was domain-restricted because the trafficking of two misprocessed mutations in the C terminus, HERG F805C and HERG R823W, was not restored by channel blockers. Our findings represent a first step toward the design of ***pharmacological*** chaperones that will rescue HERG K+ channels without block.

L7 ANSWER 2 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002151967 EMBASE
TI Allelic variants in ***long*** - ***QT*** disease genes in patients with drug-associated torsades de pointes.
AU Yang P.; Kanki H.; Drolet B.; Yang T.; Wei J.; Viswanathan P.C.; Hohnloser S.H.; Shimizu W.; Schwartz P.J.; Stanton M.; Murray K.T.; Norris K.; George Jr. A.L.; Roden D.M.
CS Dr. D.M. Roden, Department of Medicine, Division of Clinical Pharmacology, Vanderbilt Univ. School of Medicine, Nashville, TN 37232, United States. dan.roden@mcmail.vanderbilt.edu
SO Circulation, (23 Apr 2002) 105/16 (1943-1948).
Refs: 35
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
LA English
SL English
AB Background - DNA variants appearing to predispose to drug-associated "acquired" ***long*** - ***QT*** syndrome (aLQTS) have been reported in congenital ***long*** - ***QT*** disease genes. However, the incidence of these genetic risk factors has not been systematically evaluated in a large set of patients with aLQTS. We have previously identified functionally important DNA variants in genes encoding K(+) channel ancillary subunits in 11% of an aLQTS cohort. Methods and Results - The coding regions of the genes encoding the pore-forming channel proteins KvLQT1, HERG, and SCN5A were screened in (1) the same aLQTS cohort (n=92) and (2) controls, drawn from patients tolerating QT-prolonging drugs (n=67) and cross sections of the Middle Tennessee (n=71) and US populations (n=90). The frequency of three common nonsynonymous coding region polymorphisms was no different between aLQTS and control subjects, as follows: 24% versus 19% for H558R (SCN5A), 3% versus 3% for R34C (SCN5A), and 14% versus 14% for K897T (***HERG***). Missense ***mutations*** (absent in controls) were identified in 5 of 92 patients. KvLQT1 and ***HERG*** ***mutations*** (one each) reduced K(+) currents in vitro, consistent with the idea that they augment

risk for aLQTS. However, three SCN5A variants did not alter I(Na), which argues that they played no role in the aLQTS phenotype. Conclusions - DNA variants in the coding regions of congenital ***long*** - ***QT*** disease genes predisposing to aLQTS can be identified in .apprxeq. 10% to 15% of affected subjects, predominantly in genes encoding ancillary subunits.

L7 ANSWER 3 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:255073 BIOSIS
DN PREV200200255073
TI Gender differences in the ***long*** ***QT*** syndrome: Effects of beta-adrenoceptor blockade.
AU Conrath, Chantal E. (1); Wilde, Arthur A. M.; Jongbloed, Rosalie J. E.; Alders, Marielle; van Langen, Irene M.; van Tintelen, J. Peter; Doevendans, Pieter A.; Opthof, Tobias
CS (1) Department of Cardiology, University Medical Center, Heidelberglaan 100, E03.406, 3508 GA, Utrecht: c.e.conrath@med.uu.nl Netherlands
SO Cardiovascular Research, (15 February, 2002) Vol. 53, No. 3, pp. 770-776. http://www.elsevier.com/locate/cardiores. print.
ISSN: 0008-6363.
DT Article
LA English
AB Background: Gender differences have been reported in patients with the congenital ***long*** ***QT*** syndrome (LQTS). We analyzed whether electrocardiographic differences existed in females, males, girls and boys in response to beta-adrenoceptor blockade. Methods: 12-lead ECGs before and during beta-adrenoceptor blockade were collected in 87 genotyped LQTS patients (48 women, 14 men, 12 girls and 13 boys). Up to three QTc intervals were determined in each lead of the ECG. V4 was used for QT/QTc analysis. Difference between longest and shortest QT interval was taken as a measure for dispersion of QT intervals. Results: (1) Adult males had the greatest shortening of the QTc interval upon treatment with beta-adrenoceptor blockade. During treatment, adult males with LQTS1 (mutation in the KCNQ1 gene, affecting IKs current) were found to have shorter QTc intervals than adult females; this difference did not exist in LQTS2 patients (***mutation*** in the ***HERG*** gene, affecting IKr current). (2) Female LQTS2 patients had a 50% larger dispersion than female LQTS1 patients both before and during treatment. (3) Adult male LQTS1 patients constitute the only patient group with a marked decrease in QTc intervals and dispersion associated with a 100% efficacy of treatment in response to beta-adrenoceptor blockade. Conclusions: These findings indicate that, in addition to underlying differences in repolarization between men and women, cardiac electrophysiological responses to beta-adrenoceptor blockade can be modulated by gender-related factors.

L7 ANSWER 4 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002145719 EMBASE
TI [The ***long*** ***QT*** syndrome in children].
HET LANGE-QT-TIJDSYNDROOM BIJ KINDEREN.
AU Ten Harkel A.D.J.; Lubbers L.J.; Hoorntje Th.; Blom N.A.; Van Langen I.M.; Sreeram N.; Wilde A.A.M.
CS Dr. A.D.J. Ten Harkel, Kindercardioloog, Sophia Kinderziekenhuis, Afdeling Kindercardiologie, Dr. Molewaterplein 60, 3015 GJ Rotterdam, Netherlands. tenharkel@alkg.azr.nl
SO Tijdschrift voor Kindergeneeskunde, (2002) 70/2 (50-56).
Refs: 28
ISSN: 0376-7442 CODEN: TIKID4
CY Netherlands
DT Journal; Article
FS 007 Pediatrics and Pediatric Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA Dutch
SL English; Dutch
AB We examined 29 pediatric patients with ***long*** - ***Qt*** -syndrome in three academic hospitals. The mean age was 10 years (3-17). Of these patients 22 used betablocker therapy, in three combined with pacemaker. Genotyping has been performed in 22 children. LQTSI (mutation in the KCNQ1 gene) was found in twelve, LQTS2 (***mutation*** in the ***HERG*** gene) in eight and LQTS3 (mutation in the SCN5(A) gene) in two. Patients came under attention due to bradycardia postnatally in four, after near-drowning in three and after syncope in another four patients. In most of these eleven children family history was found retrospectively to be positive for sudden cardiac death or recurrent syncope. In eighteen children the diagnosis of LQTS was made during family screening. Retrospectively, six of these children were found to have had recurrent syncope. Although LQTS is becoming a well-known disease, there still are patients that come under attention after a considerable delay. This may result in sudden cardiac death that might have been prevented. Genotyping is essential in this familial disorder. There is a relation between genotype and fenotype, thus leading to differences in therapy and advice. It is also possible to diagnose asymptomatic carriers, thus enabling secondary prevention. In conclusion, LQTS has a high mortality, which can be greatly reduced by therapy. It is therefore necessary to evaluate precisely patients and family members in the case of recurrent syncope, near-drowning or sudden cardiac death. The joint management of (pediatric) cardiologist and clinical geneticist plays an important role in diagnosis and therapy.

L7 ANSWER 5 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2001:550367 BIOSIS
DN PREV200100550367
TI Drug block of IKr: Model systems and relevance to human arrhythmias.
AU Yang, Tao; Snyders, Dirk; Roden, Dan M. (1)
CS (1) Division of Clinical Pharmacology, Vanderbilt University School of Medicine, 532C Medical Research Building-I, Nashville, TN, 37232-6602: dan.roden@mcmail.vanderbilt.edu USA
SO Journal of Cardiovascular Pharmacology, (November, 2001) Vol. 38, No. 5, pp. 737-744. print.
ISSN: 0160-2446.
DT Article
LA English
SL English
AB The ***long*** ***QT*** -related arrhythmia torsades de pointes (TdP) can arise with ***mutations*** in ***HERG*** and during treatment with drugs that block cardiac IKr, the current encoded by HERG. Multiple test systems have been used to assess drug block of IKr. This study evaluated the IKr blocking potency of a series of antiarrhythmics associated with a range of clinical risks of TdP in two such systems: mouse AT-1 cells (in which IKr is the major repolarizing current) and Ltk cells transiently transfected with HERG (n=4-10 cells per drug). For each compound, the concentration required to produce 50% block of IKr or HERG tail currents (IC50) was determined. There was an excellent correlation (r=0.98, p<10-5) between values obtained in the two systems. However, the relation between the liability of a drug to cause TdP appeared dissociated from IKr blocking potency. Quinidine, dofetilide, ibutilide, procainamide, and disopyramide are all associated with TdP, but only the first three were potent blockers (IC50ltoreq1 muM), whereas procainamide and disopyramide were not (IC50>50 muM). Conversely, verapamil and amiodarone, drugs not associated with TdP, were also blockers (IC50ltoreq1 muM). We conclude that IKr blocking potency can be readily assessed in either AT-1 cells or systems in which HERG is heterologously expressed. However, not all drugs causing TdP are potent IKr blockers, and IKr block is not necessarily associated with TdP. Other properties of these drugs, therefore, contribute to their propensity to cause TdP.

L7 ANSWER 6 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001418950 EMBASE
TI Functional abnormalities of ***HERG*** ***mutations*** in ***long*** ***QT*** syndrome 2 (LQT2).
AU Hiraoka M.
CS M. Hiraoka, Dept. of Cardiovascular Diseases, Medical Res. Institute Tokyo Medical, Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. hiraoka.card@mri.tmd.ac.jp
SO Korean Journal of Physiology and Pharmacology, (2001) 5/5 (367-371).
Refs: 36
ISSN: 1226-4512 CODEN: KJPPFS
CY Korea, Republic of
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The chromosome 7-linked ***long*** ***QT*** syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (HERG) that encodes the rapidly activating delayed rectifier K(+) current, I(Kr), in cardiac myocytes. Different types of mutations have been identified in various locations of HERG channel. One of the mechanisms for the loss of normal channel function is due to membrane trafficking of channel protein. The decreased channel function in some deletion mutants appears to be due to loss of coupling with wild type HERG to form the functional channel as the tetramer. Most of missense mutants with few exceptions could interact with wild type HERG to form functional tetramer and caused dominant negative suppression with co-injection with wild type HERG showing variable effects on current amplitude, voltage dependence, and kinetics of activation and inactivation. Two missense mutants at pore regions of HERG found in Japanese LQT2 (A614V and V630L) showed accentuated inward rectification due to a negative shift in steady-state inactivation and fast inactivation. One mutation in S4 region (R534C) produced a negative shift in current activation, indicating the S4 serving as the voltage sensor and accelerated deactivation. The C-terminus mutation, S818L, could not express the current by mutant alone and did not show dominant negative suppression with co-injection of equal amount of wild type cRNA. Co-injection of excess amount of mutant with wild type produced dominant negative suppression with a shift in voltage dependent activation. Therefore, multiple mechanisms are involved in different mutations and functional abnormality in LQT2. Further characterization with the interactions between various mutants in HERG and the regulatory subunits of the channels (MiRP1 and minK) is to be clarified.

L7 ANSWER 7 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:139760 BIOSIS
DN PREV200100139760
TI Mechanisms of drug-induced correction of defective protein trafficking of ***HERG*** ***mutation*** in human ***long*** ***QT*** syndrome.

AU Zhou, Zhengfeng (1); Gong, Qiuming (1); Anderson, Corey L. (1); January, Craig T. (1)
CS (1) University of Wisconsin, Madison, WI, 53792 USA
SO Biophysical Journal, (January, 2001) Vol. 80, No. 1 Part 2, pp. 348a. print.
Meeting Info.: 45th Annual Meeting of the Biophysical Society Boston, Massachusetts, USA February 17-21, 2001 Biophysical Society
. ISSN: 0006-3495.
DT Conference
LA English
SL English

L7 ANSWER 8 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:431364 BIOSIS
DN PREV200100431364
TI Diverse mechanism of HERG K+ channel current suppression with different mutations in ***long*** ***QT*** syndrome 2.
AU Hiraoka, Masayasu (1); Nakajima, Tadashi (1); Furukawa, Tetsushi (1)
CS (1) Dept of Cardiovascular Diseases, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, 113-8510 Japan
SO Journal of Molecular and Cellular Cardiology, (June, 2001) Vol. 33, No. 6, pp. A47. print.
Meeting Info.: XVII ISHR World Congress of the International Society for Heart Research Winnipeg, Canada July 06-11, 2001
ISSN: 0022-2828.
DT Conference
LA English
SL English

L7 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 2000:98826 CAPLUS
DN 132:162048
TI Mutations in and genomic structure of HERG - a ***long*** ***QT*** syndrome gene, and ***LQT*** diagnosis
IN Keating, Mark T.; Splawski, Igor
PA University of Utah Research Foundation, USA
SO PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000006772	A1	20000210	WO 1999-US16337	19990720
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6207383	B1	20010327	US 1999-226012	19990106
AU 9951133	A1	20000221	AU 1999-51133	19990720
EP 1102863	A1	20010530	EP 1999-935710	19990720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI US 1998-122847	A	19980727		
US 1999-226012	A	19990106		
WO 1999-US16337	W	19990720		

AB The invention relates to the detn. of the genomic structure of HERG, a gene assocd. with ***long*** ***QT*** syndrome, construction of primers for ***mutational*** anal. of ***HERG*** , and newly identified ***mutations*** in ***HERG*** . Methods of diagnosis of mutations causing ***long*** ***QT*** syndrome using nucleic acid probe hybridization, single stranded conformation polymorphism technique, gene sequencing and amplification, RNAse assay are also described. Also disclosed are methods of diagnosis of ***long*** ***QT*** syndrome via immunocytochem. technique and immunoblotting with antibodies raised against a mutant HERG polypeptide, and a method of amplifying an exon of HERG using oligonucleotide primers. A method of screening for drugs useful in treating a person with ***mutation*** in ***HERG*** via measurement of a first induced K+ current in cells transformed with HERG and a transgenic animal are also provided. The sequences of the 15 intron/exon junctions has been detd. and this information is useful in devising primers for amplifying and sequencing across all of the exons of the gene. This is useful for detg. the presence or absence of mutations which are known to cause ***long*** ***QT*** syndrome. Also disclosed are many new ***mutations*** in ***HERG*** which have been found to be assocd. with ***long*** ***QT*** syndrome. Linkage anal. and phys. and genetic mapping was used to localize HERG to human chromosome 7q35-36 region. Northern blot anal. revealed that HERG is expressed mainly in heart. Combined with sequence homol. data and assocn. of mutation and ***LQT*** , it was suggested that HERG encodes .alpha.-subunit of potassium channel.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000390094 EMBASE
TI A structural basis for drug-induced ***long*** ***QT*** syndrome.
AU Mitcheson J.S.; Chen J.; Lin M.; Culberson C.; Sanguinetti M.C.
CS M.C. Sanguinetti, Eccles Institute of Human Genetics, University of Utah, Salt Lake City, UT 84112, United States. mike.sanguinetti@hci.utah.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (24 Oct 2000) 97/22 (12329-12333).
Refs: 33
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB ***Mutations*** in the ***HERG*** K+ channel gene cause inherited ***long*** ***QT*** syndrome (***LQT***), a disorder of cardiac repolarization that predisposes affected individuals to lethal arrhythmias [Curran, M. E., Splawski, I., Timothy, K. W., Vincent, G. M., Green, E. D. and Keating, M. T. (1995) Cell 80, 795-804]. Acquired ***LQT*** is far more common and is most often caused by block of cardiac HERG K+ channels by commonly used medications [Roden, D. M., Lazzara, R., Rosen, M., Schwartz, P. J., Towbin, J. and Vincent, G. M. (1996) Circulation 94, 1996-2012]. It is unclear why so many structurally diverse compounds block HERG channels, but this undesirable side effect now is recognized as a major hurdle in the development of new and safe drugs. Here we use alanine-scanning mutagenesis to determine the structural basis for high-affinity drug block of HERG channels by MK-499, a methanesulfonanilide antiarrhythmic drug. The binding site, corroborated with homology modeling, is comprised of amino acids located on the S6 transmembrane domain (G648, Y652, and F656) and pore helix (T623 and V625) of the HERG channel subunit that face the cavity of the channel. Other compounds that are structurally unrelated to MK-499, but cause ***LQT*** , also were studied. The antihistamine terfenadine and a gastrointestinal prokinetic drug, cisapride, interact with Y652 and F656, but not with V625. The aromatic residues of the S6 domain that interact with these drugs (Y652 and F656) are unique to eag/erg K+ channels. Other voltage-gated K+ (Kv) channels have Ile and Val (Ile) in the equivalent positions. These findings suggest a possible structural explanation for how so many commonly used medications block HERG but not other Kv channels and should facilitate the rational design of drugs devoid of HERG channel binding activity.

L7 ANSWER 11 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:188414 BIOSIS
DN PREV200000188414
TI HERG channel blockers can act as chemical chaperones to correct defective protein trafficking of ***HERG*** ***mutations*** in human ***long*** ***QT*** syndrome.
AU Zhou, Zhengfeng (1); Gong, Qiuming (1); January, Craig T. (1)
CS (1) University of Wisconsin, Madison, WI USA
SO Biophysical Journal, (Jan., 2000) Vol. 78, No. 1 Part 2, pp. 341A.
Meeting Info.: 44th Annual Meeting of the Biophysical Society. New Orleans, Louisiana, USA February 12-16, 2000
ISSN: 0006-3495.
DT Conference
LA English
SL English

L7 ANSWER 12 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2000:294203 BIOSIS
DN PREV200000294203
TI Drug-induced torsade de pointes: From molecular biology to bedside.
AU Tamargo, Juan (1)
CS (1) Department of Pharmacology, School of Medicine, Universidad Complutense, 28040, Madrid Spain
SO Japanese Journal of Pharmacology, (May, 2000) Vol. 83, No. 1, pp. 1-19. print.
ISSN: 0021-5198.
DT General Review
LA English
SL English
AB A progressively increasing number of cardiac and noncardiac drugs prolong the ventricular action potential duration (QT interval of the electrocardiogram) and cause a distinctive polymorphic ventricular tachycardia termed torsades de pointes (TdP) that can degenerate into ventricular fibrillation and sudden cardiac death. Drugs prolong the QT interval and cause TdP by blocking cardiac K+ channels in general and selectively blocking the rapidly activating delayed rectifier channel IKr. Coassembly of HERG (human-ether-ago-go-related gene) alpha-subunits and MiRP1 (MinK-related peptide 1) beta-subunits recapitulate the behavior of native human IKr and ***mutations*** of ***HERG*** and MiRP1 decrease the repolarizing current, delay ventricular repolarization and prolong the QT. Thus, drug-induced QT prolongation and TdP might represent an iatrogenic reproduction of the congenital LQTS. In patients with silent forms of the congenital LQTS associated with mutations in IKr, arrhythmic symptoms developed almost exclusively after exposure to QT-prolonging drugs. This review centers on the possible cellular mechanisms underlying

drug-induced QT prolongation and TdP, the description of specific drugs and risk factors facilitating the development of TdP, and the recommendations for preventing and treating this potentially fatal arrhythmia.

L7 ANSWER 13 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:13680 BIOSIS
DN PREV200000013680
TI Correction of defective protein trafficking of a mutant HERG potassium channel in human ***long*** ***QT*** syndrome: ***Pharmacological*** and temperature effects.
AU Zhou, Zhengfeng (1); Gong, Qiuming; January, Craig T. (1)
CS (1) Section of Cardiology, University of Wisconsin Hospitals and Clinics, 600 Highland Ave., Room H6/354 CSC, Madison, WI, 53792 USA
SO Journal of Biological Chemistry, (Oct. 29, 1999) Vol. 274, No. 44, pp. 31123-31126.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB The chromosome 7-linked form of congenital ***long*** ***QT*** syndrome (LQT2) is caused by mutations in the human ether-a-go-go-related gene (HERG) that encodes the rapidly activating delayed rectifier potassium channel. One mechanism for the loss of normal channel function in LQT2 is defective protein trafficking, which results in the failure of the channel protein to reach the plasma membrane. Here we show that the N470D LQT2 mutant protein is trafficking-deficient when expressed at 37 degreeC in HEK293 cells, whereas at 27 degreeC its trafficking to the plasma membrane and channel function are markedly improved. We further show that the antiarrhythmic drug E-4031, which selectively blocks HERG channels, also corrects defective protein trafficking of the N470D mutant and can restore the generation of HERG current. Similar findings were obtained with the drugs astemizole and cisapride, as well as with high concentrations of glycerol. The effect of E-4031 on HERG protein trafficking was concentration-dep endent and required low drug concentrations (saturation present at 5 muM), developed rapidly with drug exposure, and occurred post-translationally. These findings suggest that protein misfolding leading to defective trafficking of some ***HERG*** ***LQT*** ***mutations*** may be corrected by specific ***pharmacological*** strategies.

L7 ANSWER 14 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:81811 BIOSIS
DN PREV200000081811
TI Biophysical properties and molecular basis of cardiac rapid and slow delayed rectifier potassium channels.
AU Mitcheson, J. S.; Sanguinetti, M. C. (1)
CS (1) Eccles Institute of Human Genetics, University of Utah, 15 North 2030 East, Room 4220, Salt Lake City, UT USA
SO Cellular Physiology and Biochemistry, (July Oct., 1999) Vol. 9, No. 4-5, pp. 201-216.
ISSN: 1015-8987.
DT General Review
LA English
SL English
AB Normal cardiac action potential repolarization is dependent on activation of several K+ currents, including IKr and IKs. IKr activates rapidly at positive potentials, exhibits inward rectification caused by C-type inactivation, and is potently blocked by methanesulfonanilide antiarrhythmic drugs and several other common medications. IKs activates very slowly, does not inactivate and is blocked by some benzodiazepines and a chromanol. HERG encodes subunits that form channels that mediate IKr. KVLQT1 and minK encode subunits that coassemble to form channels that mediate IKs. Mutations in any of these genes cause ***long*** ***QT*** syndrome, a disorder of cardiac repolarization that predisposes individuals to lethal arrhythmias. In this review, we summarize recent studies of the biophysical and ***pharmacological*** properties of HERG and KvLQT1/minK K+ channels.

L7 ANSWER 15 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 1999:210604 BIOSIS
DN PREV199900210604
TI N-linked glycosylation sites determine HERG channel surface membrane expression.
AU Petrecca, Kevin; Atanasiu, Roxana; Akhavan, Armin; Shrier, Alvin (1)
CS (1) Department of Physiology, McGill University, 3655 Drummond Street, Montreal, PQ, H3G 1Y6 Canada
SO Journal of Physiology (Cambridge), (Feb. 15, 1999) Vol. 515, No. 1, pp. 41-48.
ISSN: 0022-3751.
DT Article
LA English
SL English
AB 1. ***Long*** ***QT*** syndrome (***LQT***) is an electrophysiological disorder that can lead to sudden death from cardiac arrhythmias. One form of ***LQT*** has been attributed to mutations in the human ether-a-go-go-related gene (HERG) that encodes a voltage-gated cardiac K+ channel. While a recent report indicates that ***LQT*** in some patients is associated with a ***mutation*** of ***HERG*** at a consensus extracellular N-linked glycosylation site (N629), earlier studies failed to identify a role for N-linked glycosylation in the functional expression of voltage-gated K+ channels. In this study we used ***pharmacological*** ***agents*** and site-directed mutagenesis to assess the contribution of N-linked glycosylation to the surface localization of HERG channels. 2. Tunicamycin, an inhibitor of N-linked glycosylation, blocked normal surface membrane expression of a HERG-green fluorescent protein (GFP) fusion protein (HERGGFP) transiently expressed in human embryonic kidney (HEK 293) cells imaged with confocal microscopy. 3. Immunoblot analysis revealed that N-glycosidase F shifted the molecular mass of HERGGFP, stably expressed in HEK 293 cells, indicating the presence of N-linked carbohydrate moieties. Mutations at each of the two putative extracellular N-linked glycosylation sites (N598Q and N629Q) led to a perinuclear subcellular localization of HERGGFP stably expressed in HEK 293 cells, with no surface membrane expression. Furthermore, patch clamp analysis revealed that there was a virtual absence of HERG current in the N-glycosylation mutants. 4. Taken together, these results strongly suggest that N-linked glycosylation is required for surface membrane expression of HERG. These findings may provide insight into a mechanism responsible for LQT2 due to N-linked glycosylation-related ***mutations*** of ***HERG*** .

L7 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2002 ACS
AN 1998:195222 CAPLUS
DN 128:228779
TI Potassium channels
AU Suessbrich, Hartmut; Busch, Andreas Eugen
CS Disease Group Cardiovascular, Hoechst Marion Roussel, Frankfurt/Main, D-65926, Germany
SO Deutsche Apotheker Zeitung (1998), 138(13), 1139-1148
CODEN: DAZEA2; ISSN: 0011-9857
PB Deutscher Apotheker Verlag
DT Journal; General Review
LA German
AB A review is given with 108 refs. on the structure, function, and ***pharmacol*** . of K channels. The heart possesses many different K+ cond.'s for the repolarization of the action potential being partly transient and partly ongoing. The significance of the individual conductivities is dependent on the cardiac frequency and the .beta.-adrenergic tonus the cond., IKs being dominant at high frequency and .beta.-adrenergic tonus. IKs was shown as an interaction of IKs proteins with KvLQT1 proteins while the human ether-a-go-go related gene protein (HERG protein) is responsible for the IKr cond. ***Mutations*** in ***HERG*** are the reason for the congenital syndromes QT-2 and QT-1. Apart from the inherited syndromes exists a drug related QT syndrome. Under certain conditions the antihistaminics terfenadine and astemizole and the antipsychotic haloperidol can lead to a prolongation of the ECG QT time partly followed by torsades de pointes, a life threatening ventricular tachycardia. The cause seems to be a retarded repolarization by HERG channel blocking. The active terfenadine metabolite fexofenadine causes no blocking thus showing no arrhythmogenic side effects.

L7 ANSWER 17 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998111183 EMBASE
TI Genetics, molecular mechanisms and management of ***long*** ***QT*** syndrome.
AU Wang Q.; Chen Q.; Towbin J.A.
CS Dr. Q. Wang, Dept. of Pediatrics (Cardiology), Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, United States. qwang@bcm.tmc.edu
SO Annals of Medicine, (1998) 30/1 (58-65).
Refs: 63
ISSN: 0785-3890 CODEN: ANMDEU
CY United Kingdom
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB Cardiac arrhythmias cause more than 300,000 sudden deaths each year in the USA alone. ***Long*** ***QT*** syndrome (***LQT***) is a cardiac disorder that causes sudden death from ventricular tachyarrhythmias, specifically torsade de pointes. Four ***LQT*** genes have been identified: KVLQT1 (LQT1) on chromosome 11p15.5, HERG (LQT2) on chromosome 7q35-36, SCN5A (LQT3) on chromosome 3p21-24, and MinK (LQT5) on chromosome 21q22. SCN5A encodes the cardiac sodium channel, and ***LQT*** -causing mutations in SCN5A lead to the generation of a late phase of inactivation-resistant whole-cell inward currents. Mexiletine, a sodium channel blocker, is effective in shortening the QT interval corrected for heart rate (QTc) of patients with SCN5A ***mutations*** . ***HERG*** encodes the cardiac I(Kr) potassium channel. ***Mutations*** in ***HERG*** act by a dominant-negative mechanism or by a loss-of-function mechanism. Raising the serum potassium concentration can increase outward HERG potassium current and is effective in shortening the QTc of patients with ***HERG*** ***mutations*** . KVLQT1 is a cardiac potassium channel protein that interacts with another small potassium channel MinK to form the cardiac I(Ks) potassium channel. Like ***HERG*** ***mutations*** , ***mutations*** in KVLQT1 and MinK can act by a dominant-negative mechanism or a loss-of-function mechanism. An effective treatment for ***LQT*** patients with KVLQT1

or MinK mutations is expected to be developed based on the functional characterization of the I(Ks) potassium channel. Genetic testing is now available for some patients with ***LQT*** .

L7 ANSWER 18 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1997:19310 BIOSIS
DN PREV199799318513
TI Molecular physiology and ***pharmacology*** of HERG: Single-channel currents and block by dofetilide.
AU Kiehn, Johann; Lacerda, Antonio E.; Wible, Barbara; Brown, Arthur M. (1)
CS (1) Rammelkamp Cent., 2500 MetroHealth Dr., Cleveland, OH 44109-1998 USA
SO Circulation, (1996) Vol. 94, No. 10, pp. 2572-2579.
ISSN: 0009-7322.
DT Article
LA English
AB Background: The human ether-a-go-go-related gene (HERG) is one locus for the hereditary ***long*** - ***QT*** syndrome. A hypothesis is that HERG produces the repolarizing cardiac potassium current I-Kr, with the consequence that ***mutations*** in ***HERG*** prolong the QT interval by reducing I-Kr. The elementary properties of HERG are unknown, and as a test of the hypothesis that HERG produces I-Kr, we compared their elementary properties. Methods and Results: We injected HERG cRNA into Xenopus oocytes and measured currents from single channels or current variance from the noise produced by ensembles of channels recorded from macro patches. Single-channel conductance was dependent on the extracellular potassium concentration ((K)-o). At physiological (K)-o, it was 2 picosiemens (pS), and at 100 mmol/L (K)-o, it was 10 pS. Openings occurred in bursts with a mean duration of 26 ms at - 100 mV. Mean open time was 3.2 ms and closed times were 1.0 and 26 ms. In excised macro patches, HERG currents were blocked by the class III antiarrhythmic drug dofetilide, with an IC-50 of 35 nmol/L. Dofetilide block was slow and greatly attenuated at positive potentials at which HERG rectifies. Conclusions: The microscopic physiology of HERG and I-Kr is similar, consistent with HERG being an important component of I-Kr. The ***pharmacology*** is also similar; dofetilide appears to primarily block activated channels and has a much lower affinity for closed and inactivated channels.

L7 ANSWER 19 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96321599 EMBASE
DN 1996321599
TI Multiple mechanisms in the ***long*** - ***QT*** syndrome: Current knowledge, gaps, and future directions.
AU Roden D.M.; Lazzara R.; Rosen M.; Schwartz P.J.; Towbin J.; Vincent G.M.
CS Division of Clinical Pharmacology, 532 Medical Research Bldg I, Vanderbilt Univ. School of Medicine,Nashville, TN 37232-6602, United States
SO Circulation, (1996) 94/8 (1996-2012).
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB The congenital ***long*** - ***QT*** syndrome (LQTS) is characterized by prolonged QT intervals, QT interval lability, and polymorphic ventricular tachycardia. The manifestations of the disease vary, with a high incidence of sudden death in some affected families but not in others. Mutations causing LQTS have been identified in three genes, each encoding a cardiac ion channel. In families linked to chromosome 3, mutations in SCN5A, the gene encoding the human cardiac sodium channel, cause the disease. Mutations in the human ether-a- go-go-related gene (HERG), which encodes a delayed-rectifier potassium channel, cause the disease in families linked to chromosome 7. Among affected individuals in families linked to chromosome 11, mutations have been identified in KVLQT1, a newly cloned gene that appears to encode a potassium channel. The SCN5A mutations result in defective sodium channel inactivation, whereas ***HERG*** ***mutations*** result in decreased outward potassium current. Either mutation would decrease net outward current during repolarization and would thereby account for prolonged QT intervals on the surface ECG. Preliminary data suggest that the clinical presentation in LQTS may be determined in part by the gene affected and possibly even by the specific mutation. The identification of disease genes in LQTS not only represents a major milestone in understanding the mechanisms underlying this disease but also presents new opportunities for combined research at the molecular, cellular, and clinical levels to understand issues such as adrenergic regulation of cardiac electrophysiology and mechanisms of susceptibility to arrhythmias in LQTS and other settings.

L7 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1996:332645 BIOSIS
DN PREV199699055001
TI High affinity open channel block by dofetilide of HERG expressed in a human cell line.
AU Snyders, Dirk J.; Chaudhary, Archana
CS Dep. Med., 554-MRB2, Vanderbilt Univ. Sch. Med., Nashville, TN 37232-6602 USA
SO Molecular Pharmacology, (1996) Vol. 49, No. 6, pp. 949-955.
ISSN: 0026-895X.
DT Article
LA English
AB In the ***long*** ***QT*** syndrome, excessive prolongation of the cardiac action potential leads to polymorphic ventricular tachycardia (torsades de pointes) and sudden death. ***Mutations*** in ***HERG*** have been identified as one of the causes of the chromosome 7-linked form of congenital ***long*** ***QT*** syndrome. The biophysical properties of currents recorded from HERG expressing Xenopus oocytes are similar to those of a cardiac K+ current, I-Kr, but the characteristic nanomolar methanesulfonanilide sensitivity has not been demonstrated. To determine the biophysical and ***pharmacological*** properties of HERG under experimental conditions similar to those used to study native cardiac currents, we examined currents expressed after expression of HERG in a human cell line, human embryonic kidney 293. Transfected cells displayed K+-selective outward currents that activated at membrane potentials positive to -50 mV with strongly voltage-dependent kinetics (time constant (tau) = 2 sec at -20 mV and 188 msec at +20 mV). Marked inward rectification was observed for depolarizations positive to +0 mV, which was due to rapid channel inactivation (tau = 6 msec at +50 mV). The subsequent tail currents at -40 mV displayed an initial rising phase with tau = 10 msec, followed by a slow multiexponential decline. The EC-50 for the methanesulfonanilide I-Kr blocker dofetilide was 12 +- 2 nM. Induction of block depended on depolarization beyond the threshold for channel opening. Time-dependent block developed slowly, with tau = 5.2 +- 0.6 sec (300 nM) at + 10 mV, and was delayed by stronger depolarizations. This pattern suggested that dofetilide preferentially blocks open (or activated) channels and that the fast inactivation may competitively slow the binding kinetics. The latter occurrence was further supported by a simplified mathematical model that addressed the impact on binding kinetics of fast inactivation. These results indicate that the HERG gene product encodes an alpha subunit that, when expressed in mammalian cells, displays both the major functional and ***pharmacological*** properties of native I-Kr. Dofetilide acts as a slow-onset/slow-offset open channel blocker of this current at nanomolar concentrations.

L7 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 1996:160519 BIOSIS
DN PREV199698732654
TI Class III antiarrhythmic drugs block HERG, a human cardiac delayed rectifier K+ channel: Open-channel block by methanesulfonanilides.
AU Spector, Peter S.; Curran, Mark E.; Keating, Mark T.; Sanguinetti, Michael C. (1)
CS (1) Cardiol. Div., Univ. Utah Health Sci. Cent., Salt Lake City, UT 84112 USA
SO Circulation Research, (1996) Vol. 78, No. 3, pp. 499-503.
ISSN: 0009-7330.
DT Article
LA English
AB We recently reported that ***mutations*** in ***HERG*** , a potassium channel gene, cause ***long*** ***QT*** syndrome. Heterologous expression of HERG in Xenopus oocytes revealed that this channel had biophysical properties nearly identical to a cardiac delayed rectifier K+ current, I-Kr, but had dissimilar ***pharmacological*** properties. Class III antiarrhythmic drugs such as E-4031 and MK-499 are potent and specific blockers of I-Kr in cardiac myocytes. Our initial studies indicated that these compounds did not block HERG at a concentration of 1 mu-mol/L. In the present study, we used standard two-microelectrode voltage-clamp techniques to further characterize the effects of these drugs on HERG channels expressed in oocytes. Consistent with initial findings, 1 mu-mol/L MK-499 and E-4031 had no effect on HERG when oocytes were voltage clamped at a negative potential and not pulsed during equilibration with the drug. However, MK-499 did block HERG current if oocytes were repetitively pulsed, or clamped at a voltage positive to the threshold potential for channel activation. This finding is in contrast to previous studies that showed significant block of I-Kr in isolated myocytes by similar drugs, even in the absence of pulsing. This apparent discrepancy may be due to differences in channel characteristics (HERG versus guinea pig and mouse I-Kr), tissue (oocytes versus myocytes), or specific drugs. Under steady state conditions, block of HERG by MK-499 was half maximal at 123 +- 12 nmol/L at a test potential of -20 mV. MK-499 (150 nmol/L) did not affect the voltage dependence of activation and rectification nor the kinetics of activation and deactivation of HERG. These data indicate that MK-499 preferentially blocks open HERG channels and further support the conclusion that HERG subunits form I-Kr channels in cardiac myocytes.

L7 ANSWER 22 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96074248 EMBASE
DN 1996074248
TI Mechanisms and management of congenital and acquired ***long*** ***QT*** syndromes.
AU Lazzara R.
CS Cardiovascular Section, University of Oklahoma, Health Sciences Center, 920 Stanton L. Young,Oklahoma City, OK 73104, United States
SO Archives des Maladies du Coeur et des Vaisseaux, (1996) 89/SPEC. ISSUE I (51-55).
ISSN: 0003-9683 CODEN: AMCVAN
CY France

DT Journal; Conference Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English; French
AB The ***long*** ***QT*** syndromes can be divided into congenital and acquired forms. Early afterdepolarizations have been identified as triggering mechanisms for both congenital and acquired QT syndromes but reentry may play a role in the perpetuation of the ventricular tachycardia, torsade de pointes. Studies of the ionic mechanisms of early afterdepolarizations have implicated L-type Ca2+ current, persisting Na+ current, and Na+:Ca2+ exchange current related to Ca2+ loading. Different ionic mechanisms may be operative in early afterdepolarizations occuring at different levels of membrane potential in the setting of prolonged repolarization by blocking K+ currents or maintaining non-inactivating Ca2+ or Na+ currents or in early afterdepolarizations due to adrenergic stimulation. In the congenital ***long*** ***QT*** syndromes, two mutations have recently been discovered in the genes SCN5A and HERG which encode respectively the Na+ channel and a K+ channel conducting the current I(kr). It is postulated that the SCN5A mutation leads to a problem with inactivation of Na+ current. In the case of the ***HERG*** ***mutation*** , the K+ current appears to be diminished. In the case of the acquired ***long*** ***QT*** syndromes, the therapeutic challenge is to maintain the prolonged repolarization but to interrupt the arrhythmogenic cascade. Current therapies for torsades de pointes include speeding of the heart rate, which enhances K+ current, and Ca2+ blockers or Mg, also a Ca2+ blocker. In the congenital ***long*** ***QT*** syndromes, therapy in the past has been directed toward reducting adrenergic influence either by betablockade or left cardiac sympathectomy. Recent discoveries open other possibilities such as Na+ channel blockers and methods to increase I(kr) such as elevation of extracellular K+.

=> d his

(FILE 'HOME' ENTERED AT 11:46:48 ON 06 JUN 2002)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:47:01 ON 06 JUN 2002
L1 1331 S HERG OR HUMAN ETHER A-GO-GO GENE
L2 4523 S LONG QT OR LQT
L3 569 S L1 AND L2
L4 281 S L1 (3A) MUTAT?
L5 244 S L4 AND L2
L6 36 S L5 AND (DRUG SCREEN? OR AGENT? OR PHARMAC?)
L7 22 DUP REM L6 (14 DUPLICATES REMOVED)

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1 FILES SEARCHED...
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PROCESSING COMPLETED FOR L8
L9 53 DUP REM L8 (45 DUPLICATES REMOVED)

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=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 53 ANSWERS - CONTINUE? Y/(N):y

L9 ANSWER 1 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 1998:490886 BIOSIS
DN PREV199800490886
TI A K+ channel splice variant common in human heart lacks a C-terminal domain required for expression of rapidly activating delayed rectifier current.
AU Kupershmidt, Sabina; Snyders, Dirk J.; Raes, Adam; Roden, Dan M. (1)
CS (1) Dep. Pharmacol., 532 Medical Research Build. I, Vanderbilt Univ. Sch. Med., Nashville, TN 37232-6602 USA
SO Journal of Biological Chemistry, (***Oct. 16, 1998***) Vol. 273, No. 42, pp. 27231-27235.
ISSN: 0021-9258.
DT Article
LA English
AB We have cloned HERGUSO, a C-terminal splice variant of the human ether-a-go-go-related gene (HERG), the gene encoding the rapid component of the delayed rectifier (IKr), from human heart, and we find that its mRNA is apprx 2-fold more abundant than that for HERG1 (the originally described cDNA). After transfection of HERGUSO in Ltk- cells, no current was observed. However, coexpression of HERGUSO with HERG1 modified IKr by
decreasing its amplitude, accelerating its activation, and shifting the voltage dependence of activation 8.8 mV negative. As with HERGUSO, HERGDELTAC (a HERG1 construct lacking the C-terminal 462 amino acids) also
produced no current in transfected cells. However, IKr was rescued by ligation of 104 amino acids from the C terminus of HERG1 to the C terminus of HERGDELTAC, indicating that the C terminus of HERG1 includes a domain (Itoreq 104 amino acids) that is critical for faithful recapitulation of IKr. The lack of this C-terminal domain not only explains the finding that HERGUSO does not generate IKr but also indicates a similar mechanism for hither-to-uncharacterized ***long*** ***QT*** syndrome ***HERG*** ***mutations*** that disrupt the splice site or the C-terminal. We suggest that the amplitude and gating of cardiac IKr depends on expression of both BERG1 and HERGUSO.

L9 ANSWER 2 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 1998:400847 BIOSIS
DN PREV199800400847
TI HERG channel dysfunction in human ***long*** ***QT*** syndrome. Intracellular transport and functional defects.
AU Zhou, Zhengfeng; Gong, Qiuming; Epstein, Miles L.; January, Craig T. (1)
CS (1) Dep. Med., Univ. Wisconsin Hosp. Clinics, Room H6/352, 600 Highland Ave., Madison, WI 53792 USA
SO Journal of Biological Chemistry, (***Aug. 14, 1998***) Vol. 273, No. 33, pp. 21061-21066.
ISSN: 0021-9258.
DT Article
LA English
AB ***Mutations*** in ***HERG*** are associated with human chromosome 7-linked congenital ***long*** ***QT*** (***LQT*** -2) syndrome. We used electrophysiological, biochemical, and immunohistochemical methods to study the molecular mechanisms of HERG channel dysfunction caused by ***LQT*** -2 ***mutations*** . Wild type ***HERG*** and ***LQT*** -2 ***mutations*** were studied by stable and transient expression in HEK 293 cells. We found that some mutations (Y611H and V822M) caused defects in biosynthetic processing of HERG channels with the protein retained in the endoplasmic reticulum. Other mutations (I593R and G628S) were processed similarly to wild type ***HERG*** protein, but these ***mutations*** did not produce functional channels. In contrast, the T4741 ***mutation*** expressed ***HERG*** current but with altered gating properties. These findings suggest that the loss of HERG channel function in ***LQT*** -2 mutations is caused by multiple mechanisms including abnormal channel processing, the generation of nonfunctional channels, and altered channel gating.

L9 ANSWER 3 OF 53 CAPLUS COPYRIGHT 2002 ACS
AN 1998:195222 CAPLUS
DN 128:228779
TI Potassium channels
AU Suessbrich, Hartmut; Busch, Andreas Eugen
CS Disease Group Cardiovascular, Hoechst Marion Roussel, Frankfurt/Main, D-65926, Germany
SO Deutsche Apotheker Zeitung (***1998***), 138(13), 1139-1148
CODEN: DAZEA2; ISSN: 0011-9857
PB Deutscher Apotheker Verlag
DT Journal; General Review
LA German
AB A review is given with 108 refs. on the structure, function, and pharmacol. of K channels. The heart possesses many different K+ cond.'s for the repolarization of the action potential being partly transient and partly ongoing. The significance of the individual conductivities is dependent on the cardiac frequency and the .beta.-adrenergic tonus the cond., IKs being dominant at high frequency and .beta.-adrenergic tonus. IKs was shown as an interaction of IKs proteins with KvLQT1 proteins while the human ether-a-go-go related gene protein (HERG protein) is responsible for the IKr cond. ***Mutations*** in ***HERG*** are the reason for the congenital syndromes QT-2 and QT-1. Apart from the inherited syndromes exists a drug related QT syndrome. Under certain conditions the antihistaminics terfenadine and astemizole and the antipsychotic haloperidol can lead to a prolongation of the ECG QT time partly followed by torsades de pointes, a life threatening ventricular tachycardia. The cause seems to be a retarded repolarization by HERG channel blocking. The active terfenadine metabolite fexofenadine causes no blocking thus showing no arrhythmogenic side effects.

L9 ANSWER 4 OF 53 CAPLUS COPYRIGHT 2002 ACS
AN 1999:36515 CAPLUS
DN 130:221423
TI Alteration of HERG current profile during the cardiac ventricular action potential, following a pore mutation
AU Hancox, Jules C.; Witchel, Harry J.; Varghese, Anthony
CS Department of Physiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SO Biochemical and Biophysical Research Communications (***1998***), 253(3), 719-724
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB HERG is believed to encode the major subunit of the cardiac "rapid" delayed rectifier K channel (IKr). Both IKr and HERG exhibit marked inward rectification at pos. membrane potentials due to rapid inactivation and this is thought to influence significantly the contribution of the current to cardiac action potential (AP) repolarization. The authors

investigated directly the role played by rapid inactivation, by measuring current activated by a ventricular AP waveform, from Chinese Hamster Ovary cells transfected with HERG cDNA with a point mutation (S631A) in the pore region. Square command pulses elicited HERG-S631A current which increased progressively in magnitude with test potential up to +30/+40 mV. During test pulses to +40mV, HERG-S631A exhibited little inactivation compared to wild-type HERG. During an action potential command, WT-HERG current developed progressively during the AP plateau and slow repolarization phase, showing maximal current between -30mV and -40mV. In contrast, HERG-S631A current increased earlier during the AP plateau, with a maximal amplitude near +30mV. Current then declined as the AP proceeded, giving rise to a "bow" - or "inverted-U-" shaped current profile. A math. model with inactivation removed from the HERG current reproduced the I-V profile of HERG-S631A. These data provide a direct demonstration that rapid inactivation normally plays a crit. role in detg. both time-course and voltage dependence of HERG/IKr-current during the cardiac ventricular AP. (c) 1998 Academic Press.

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L9 ANSWER 5 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

AN 1998:474867 BIOSIS
DN PREV199800474867
TI Inhibition of cardiac delayed rectifier K+ current by overexpression of the ***long*** - ***QT*** syndrome ***HERG*** G628S ***mutation*** in transgenic mice.
AU Babij, Philip; Askew, G. Roger; Nieuwenhuijsen, Bart; Su, Chien-Min; Bridal, Terry R.; Jow, Brian; Argentieri, Thomas M.; Kulik, John; Degennaro, Louis J.; Spinelli, Walter; Colatsky, Thomas J. (1)
CS (1) Wyeth-Ayerst Res., PO Box 42528, Philadelphia, PA 19101-2528 USA
SO Circulation Research, (***Sept. 21, 1998***) Vol. 83, No. 6, pp. 668-678.
ISSN: 0009-7330.
DT Article
LA English
AB ***Mutations*** in the ***HERG*** gene are linked to the LQT2 form of the inherited ***long*** - ***QT*** syndrome. Transgenic mice were generated expressing high myocardial levels of a particularly severe form of LQT2-associated ***HERG*** ***mutation*** (G628S). Hearts from G628S mice appeared normal except for a modest enlargement seen only in females. Ventricular myocytes isolated from adult wild-type hearts consistently exhibited an inwardly rectifying E-4031-sensitive K+ current resembling the rapidly activating cardiac delayed rectifier K+ current (IKr) in its time and voltage dependence; this current was not found in cells isolated from G628S mice. Action potential duration was significantly prolonged in single myocytes from G628S ventricle (cycle length = 1 second, 26degree C) but not in recordings from intact ventricular strips studied at more physiological rates and temperature (200 to 400 bpm, 37degree C). ECG intervals, including QT duration, were unchanged, although minor aberrancies were noted in 20% (16/80) of the G628S mice studied, primarily involving the QRS complex and, more rarely, T-wave morphology. The aberrations were more commonly observed in females than males but could not be correlated with sex-based differences in action potential duration. These results establish the presence of IKr in the adult mouse ventricle and demonstrate the ability of the G628S mutation to exert a dominant negative effect on endogenous IKr in vivo, leading to the expected LQT2 phenotype of prolonged repolarization at the single cell level but not QT prolongation in the intact animal. The model may be useful in dissecting repolarization currents in the mouse heart and as a means of examining the mechanisms by which the G628S mutation exerts its dominant negative effect on native cardiac cells in vivo.

L9 ANSWER 6 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:404662 BIOSIS
DN PREV199800404662
TI RsaI and MaeI intragenic RFLPs in the human HERG gene.
AU Fung, D.; Zhang, L.; French, J.; Bailey, B.; Trent, R. J. (1)
CS (1) Dep. Molecular Clinical Genetics, Royal Prince Alfred Hosp., Missenden Rd., Camperdown, NSW 2050 Australia
SO Clinical Genetics, (***June, 1998***) Vol. 53, No. 6, pp. 504.
ISSN: 0009-9163.
DT Article
LA English

L9 ANSWER 7 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1998:524152 BIOSIS
DN PREV199800524152
TI Rapid detection of mutations in the ***long*** - ***QT*** syndrome by using fluorescence-based single-strand conformation polymorphism analysis.
AU Wedekind, H. (1); Schulze-Bahr, E. (1); Haverkamp, W. (1); Foppe, B.; Moennig, G. (1); Borggrefe, M. (1); Funke, H.; Breithardt, G. (1)
CS (1) Dep. Cardiol. and Angiol., Hosp. Univ. Muenster, Muenster Germany
SO European Heart Journal, (***Aug., 1998***) Vol. 19, No. ABST. SUPPL., pp. 484.
Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology
. ISSN: 0195-668X.
DT Conference
LA English

L9 ANSWER 8 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1999:524195 BIOSIS
DN PREV199900524195
TI The loss of function induced by ***HERG*** and KVLQT1 ***mutations*** does not correlate with the clinical severity of the ***Long*** ***QT*** Syndrome.
AU Priori, Silvia G. (1); Napolitano, Carlo (1); Brown, Arthur M.; Bianchi, Laura; Taglialatela, Maurizio; Ronchetti, Elena; Castaldo, Pasqualina; Bloise, Raffaella; Schwartz, Peter J.
CS (1) Fondazione S. Maugeri, Pavia Italy
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I457.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 9 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

AN 1998:271690 BIOSIS
DN PREV199800271690
TI Genomic organization and ***mutational*** analysis of ***HERG*** , a gene responsible for familial ***long*** ***QT*** syndrome.
AU Itoh, Toshio; Tanaka, Toshihiro (1); Nagai, Ryozo; Kamiya, Tetsuro; Sawayama, Toshitami; Nakayama, Toshio; Tomoike, Hitonobu; Sakurada, Harumizu; Yazaki, Yoshio; Nakamura, Yusuke
CS (1) Lab. Mol. Med., Human Genome Cent., Inst. Med. Sci., Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108 Japan
SO Human Genetics, (***April, 1998***) Vol. 102, No. 4, pp. 435-439.
ISSN: 0340-6717.
DT Article
LA English
AB Familial ***long*** ***QT*** syndrome (LQTS) is characterized by prolonged ventricular repolarization. Clinical symptoms include recurrent syncopal attacks, and sudden death may occur as a result of ventricular tachyarrhythmias. Three genes responsible for this syndrome (KVLQT1, HERG, and SCN5A) have been identified so far, and mutations have been reported on the basis of partially characterized genomic organization. To optimize the search for ***HERG*** ***mutations*** , we have determined the genomic structure of ***HERG*** and investigated ***mutations*** in LQTS families. Human genomic clones containing the HERG gene were isolated from a human genomic library by using reverse-transcribed polymerase chain reaction (RT-PCR) products from this gene as probes. We determined exon/intron boundaries and flanking intronic sequences by using primers synthesized on the basis of the HERG cDNA sequence available in the DNA database. HERG was shown to consist of 15 exons spanning approximately 19 kb on chromosome 7q35. Subsequently, we synthesized oligonucleotide primers to cover the entire coding region and searched for mutations in 36 Japanese LQTS families. When genomic DNA from each proband was examined by the PCR/single-strand conformation polymorphism technique followed by direct DNA sequencing, five novel mutations were detected. Each mutation was present in affected relatives of the respective proband. This work should increase the efficiency of screening ***mutations*** associated with ***HERG*** .

L9 ANSWER 10 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

AN 1998:430301 BIOSIS
DN PREV199800430301
TI Novel mechanism of HERG current suppression in LQT2: Shift in voltage dependence of HERG inactivation.
AU Nakajima, Tadashi; Furukawa, Tetsushi; Tanaka, Toshihiro; Katayama, Yoshifumi; Nagai, Ryozo; Nakamura, Yusuke; Hiraoka, Masayasu (1)
CS (1) Dep. Cardiovasc. Dis., Med. Res. Inst., Tokyo Med. Dent. Univ., 1-5-45 Yushima, Bunkyo-ku, Tokyo-113 Japan
SO Circulation Research, (***Aug. 24, 1998***) Vol. 83, No. 4, pp. 415-422.
ISSN: 0009-7330.
DT Article
LA English
AB In a Xenopus oocyte heterologous expression system, we characterized the electrophysiology of 3 novel missense ***mutations*** of ***HERG*** identified in Japanese LQT2 families: T474I (within the S2-S3 linker), A614V, and V630L (in the outer mouth of pore-forming region). For each of the 3 mutations, injection of mutant cRNA alone did not express detectable currents. Coinjection of wild-type (WT) along with each mutant cRNA (T474I/WT, A614V/WT, and V630L/WT) suppressed HERG current in a dominant-negative manner, and the order of magnitude of current suppression was V630L/WT>A614V/WT>T474I/WT. In addition to decreases in slope conductance for all 3 mutants, the voltage dependence of steady-state inactivation was shifted to negative potentials for V630L/WT and A614V/WT. Consequently, channel availability at positive potentials was diminished, and inward rectification was enhanced for these 2 mutants. Thus, missense ***mutations*** of ***HERG*** caused dominant-negative suppression through multiple mechanisms. The shift in voltage dependence of HERG inactivation and the resulting enhanced inward

rectification in A614V/WT and V630L/WT provide a novel mechanism for suppression of the HERG current carrying outward current during the repolarization phase of the action potential.

L9 ANSWER 11 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:149500 BIOSIS
DN PREV199800149500
TI Cardiac events in genotyped ***long*** ***QT*** syndrome patients.
AU Zareba, W.; Moss, A. J.; Robinson, J.; Schwartz, P. J.; Vincent, G. M.; Priori, S. G.; Benhorin, J.; Locati, E. H.; Towbin, J. A.; Keating, M. T.; Lehmann, M. H.; Hall, W. J.; Napolitano, C.; Andrews, M.; Zhang, L.; Timothy, K.
CS Univ. Rochester, Rochester, NY USA
SO Journal of the American College of Cardiology, (***Feb., 1998***) Vol. 31, No. 2 SUPPL. A, pp. 349A.
Meeting Info.: 47th Annual Scientific Session of the American College of Cardiology Atlanta, Georgia, USA March 29-April 1, 1998 The American College of Cardiology
. ISSN: 0735-1097.
DT Conference
LA English

L9 ANSWER 12 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 1998:228168 BIOSIS
DN PREV199800228168
TI Multiple different missense mutations in the pore region of HERG in patients with ***long*** ***QT*** syndrome.
AU Satler, Carol Ann; Vesely, Mark R.; Duggal, Priya; Ginsburg, Geoffrey S.; Beggs, Alan H. (1)
CS (1) Genetics Div., Children's Hosp., 300 Longwood Ave., Boston, MA 02115 USA
SO Human Genetics, (***March, 1998***) Vol. 102, No. 3, pp. 265-272.
ISSN: 0340-6717.
DT Article
LA English
AB ***Long*** ***QT*** syndrome (LQTS), is an inherited cardiac disorder in which ventricular tachyarrhythmias predispose affected individuals to syncope, seizures, and sudden death. Characteristic electrocardiographic findings include a prolonged QT interval, T wave alternans, and notched T waves. We have screened LQTS patients from 89 families for mutations in the pore region of HERG , the K+ channel gene previously associated with chromosome 7-linked LQT2. In six unrelated LQTS kindreds, single-strand conformation polymorphism analyses identified aberrant conformers in all affected family members. These conformers were not seen in over 100 unaffected, unrelated control individuals, suggesting that they represent pathogenic LQTS mutations. DNA sequence analyses of the aberrant conformers demonstrated that they reflect five different missense mutations: V612L, A614V, N629D, N629S, and N633S. The missense mutation A614V was found in two unrelated families. Further functional studies will be required to determine what effect each of these changes may have on HERG channel function.

L9 ANSWER 13 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:176820 BIOSIS
DN PREV199800176820
TI The ***long*** ***QT*** syndrome: Ion channel diseases of the heart.
AU Ackerman, Michael J. (1)
CS (1) Dep. Pediatric Adolescent Med., Mayo Clinic Rochester, 200 First St. SW, Rochester, MN 55905 USA
SO Mayo Clinic Proceedings, (***March, 1998***) Vol. 73, No. 3, pp. 250-269.
ISSN: 0025-6196.
DT General Review
LA English
AB Once limited to discussions of the Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome, the ***long*** ***QT*** syndrome (LQTS) is now understood to be a collection of genetically distinct arrhythmogenic cardiovascular disorders resulting from mutations in fundamental cardiac ion channels that orchestrate the action potential of the human heart. Our understanding of this genetic "channelopathy" has increased dramatically from electro- cardiographic depictions of marked QT interval prolongation and torsades de pointes and clinical descriptions of people experiencing syncope and sudden death to molecular revelations in the 1990s of perturbed ion channel genes. More than 35 mutations in four cardiac ion channel genes-KVLQT1 (voltage-gated K channel gene causing one of the autosomal dominant forms of LQTS) (LQT1), HERG (human ether-a-go-go related gene) (LQT2), SCN5A (LQT3), and KCNE1 (minK, LQT5)-have been identified in LQTS. These genes encode ion channels responsible for three of the fundamental ionic currents in the cardiac action potential. These exciting molecular breakthroughs have provided new opportunities for translational research with investigations into genotype-phenotype correlations and gene-targeted therapies.

L9 ANSWER 14 OF 53 CAPLUS COPYRIGHT 2002 ACS
AN 1998:379684 CAPLUS
DN 129:173726
TI Disorders associated with K channel abnormalities
AU Yamashita, Naohide
CS Dep. Advanced Medical Science, Inst. Med. Sci., Univ. Tokyo, Tokyo, 108-8639, Japan
SO Shinkei Kenkyu no Shinpo (***1998***), 42(2), 224-233
CODEN: SKNSAF; ISSN: 0001-8724
PB Igaku Shoin Ltd.
DT Journal; General Review
LA Japanese
AB A review with 22 refs. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), ***long*** ***QT*** syndrome, Bartter's syndrome and episodic ataxia/myokymia syndrome are caused by mutations of the potassium channel genes. Abnormalities of potassium channel genes are also explored in non-insulin dependent diabetes mellitus (NIDDM), although definite assocns. between NIDDM and the potassium channel gene mutations have not been established. In PHHI there are mutations in the second nucleotide binding fold (NBF-2) of the SUR gene and the normal NFB-2 is not formed. Consequently the function of KATP is impaired, which causes hyperinsulinemia. Type 1 ***long*** ***QT*** syndrome is ascribed to missense mutations or to the intragenic deletion in the KvLQT1 gene, whereas type 2 long QTY syndrome is caused by missense ***mutations*** in the ***HERG*** gene. Abnormalities of these genes prolong the repolarizing phase of action potentials in cardiac muscles and the lethal arrhythmias, such as torsade de pointes polymorphic ventricular tachycardia, occur. Class III antiarrhythmic drugs, antihistamines, and antifungal drugs also inhibit HERG channels. The ***long*** ***QT*** syndrome caused by these drugs is categorized as the acquired one. Type 3 ***long*** ***QT*** syndrome is linked to the cardiac sodium channel gene (SCN5A). In addn. to the mutations in the Na-K-2Cl cotransporter gene, mutations in ROMK gene are responsible for Bartter's syndrome, indicating that there are heterogeneities in Bartter's syndrome. The loss of ROMK function results in the low potassium concn. in the lumen and Na-K-2Cl cotransport activities are impaired. Thus the clin. features of the ROMK gene abnormalities (salt wasting, hypokalemic alkalosis, hypercalciuria, low blood pressure) are similar to those of the Bartter's syndrome ascribed to the mutations in the Na-K-2Cl cotransporter gene. Mutations in the KCNA1 gene in the heterozygous state are reported in episodic ataxia/myokymia syndrome. In Alzheimer disease .beta.-amyloid peptide (.beta.-AP) accumulates in brain and their aggregations have been suggested to be one factor leading to senile plaque formation. In hippocampal neurons .beta.-AP affects fast-inactivating potassium channels or delayed potassium channels. Alterations of potassium channels affect intracellular calcium concn., synaptogenesis and synaptic plasticity, which may be assocd. with the pathophysiol. of Alzheimer disease. In rat cortical astrocytes .beta.-AP induces morphol. changes coincide with increased potassium and chloride currents. These changes in astrocytes may account for brain astrocytosis obsd. in Alzheimer disease. Thyroid hormone enhance the inward rectifying potassium current in ventricular myocytes, which may explain the shortening of the action potential duration in hyperthyroidism. It has also been reported that inward rectifying potassium currents are lost in human glial cells of diseased retina. Thus abnormalities of potassium channels are assocd. with many diseases.

L9 ANSWER 15 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1998:93336 BIOSIS
DN PREV199800093336
TI Novel missense ***mutation*** (G601S) of ***HERG*** in a Japanese ***long*** ***QT*** syndrome family.
AU Akimoto, Kaoru; Furutani, Michiko; Imamura, Shin-Ichiro; Furutani, Yoshiyuki; Kasanuki, Hiroshi; Takao, Atsuyoshi; Momma, Kazuo; Matsuoka, Rumiko (1)
CS (1) Dep. Pediatr. Cardiol., Heart Inst. Japan, Tokyo Women's Med. Coll., 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162 Japan
SO Human Mutation, (1998) Vol. 0, No. SUPPL. 1, pp. S184-S186.
ISSN: 1059-7794.
DT Article
LA English

L9 ANSWER 16 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1998:391855 BIOSIS
DN PREV199800391855
TI Genomic structure of three ***long*** ***QT*** syndrome genes: KVLQT1, HERG, and KCNE1.
AU Splawski, Igor (1); Shen, Jiaxiang; Timothy, Katherine W.; Vincent, G. Michael; Lehmann, Michael H.; Keating, Mark T. (1)
CS (1) Eccles Inst. Hum. Genet., 15 N 2030 E Room 6110B, Univ. Utah, Salt Lake City, UT 84112 USA
SO Genomics, (***July 1, 1998***) Vol. 51, No. 1, pp. 86-97.
ISSN: 0888-7543.
DT Article
LA English
AB ***Long*** ***QT*** syndrome (***LQT***) is a cardiac disorder causing syncope and sudden death from arrhythmias. ***LQT*** is characterized by prolongation of the QT interval on electrocardiogram, an indication of abnormal cardiac repolarization. ***Mutations*** in KVLQT1, ***HERG*** , SCN5A, and KCNE1, genes encoding cardiac ion channels, cause ***LQT*** . Here, we define the complete genomic structure of three ***LQT*** genes and use this information to identify disease-associated mutations. KVLQT1 is composed of 16 exons and encompasses approximately 400 kb. HERG consists of 16 exons and spans 55

kb. Three exons make up KCNE1. Each intron of these genes contains the invariant GT and AG at the donor and acceptor splice sites, respectively. Intron sequences were used to design primer pairs for the amplification of all exons. Familial and sporadic cases affected by ***mutations*** in KVLQT1, ***HERG*** , and KCNE1 can now be genetically screened to identify individuals at risk of developing this disorder. This work has clinical implications for presymptomatic diagnosis and therapy.

L9 ANSWER 17 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 1998:223757 BIOSIS
DN PREV199800223757
TI Genetics, molecular mechanisms and management of ***long*** ***QT*** syndrome.
AU Wang, Qing (1); Chen, Qiuyun; Towbin, Jeffrey A.
CS (1) Dep. Pediatr., Baylor Coll. Med., One Baylor Plaza, Room 333E, Houston, TX 77030 USA
SO Annals of Medicine, (***Feb., 1998***) Vol. 30, No. 1, pp. 58-65.
ISSN: 0785-3890.
DT General Review
LA English
AB Cardiac arrhythmias cause more than 300 000 sudden deaths each year in the USA alone. ***Long*** ***QT*** syndrome (***LQT***) is a cardiac disorder that causes sudden death from ventricular tachyarrhythmias, specifically torsade de pointes. Four ***LQT*** genes have been identified: KVLQT1 (LQT1) on chromosome 11p15.5, HERG (LQT2) on chromosome 7q35-36, SCN5A (LQT3) on chromosome 3p21-24, and MinK (LQT5) on chromosome 21q22. SCN5A encodes the cardiac sodium channel, and ***LQT*** -causing mutations in SCN5A lead to the generation of a late phase of inactivation-resistant whole-cell inward currents. Mexiletine, a sodium channel blocker, is effective in shortening the QT interval corrected for heart rate (QTc) of patients with SCN5A ***mutations*** . ***HERG*** encodes the cardiac IKr potassium channel. ***Mutations*** in ***HERG*** act by a dominant-negative mechanism or by a loss-of-function mechanism. Raising the serum potassium concentration can increase outward HERG potassium current and is effective in shortening the QTc of patients with ***HERG*** ***mutations*** . KVLQT1 is a cardiac potassium channel protein that interacts with another small potassium channel MinK to form the cardiac IKs potassium channel. Like ***HERG*** ***mutations*** , ***mutations*** in KVLQT1 and MinK can act by a dominant-negative mechanism or a loss-of-function mechanism. An effective treatment for ***LQT*** patients with KVLQT1 or MinK mutations is expected to be developed based on the functional characterization of the IKs potassium channel. Genetic testing is now available for some patients with ***LQT*** .

L9 ANSWER 18 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:513966 BIOSIS
DN PREV199900513966
TI A novel missense ***mutation*** L564P in ***HERG*** potassium channel in a French Canadian ***Long*** ***QT*** syndrome family.
AU St-Pierre, Julie (1); Blier, Louis; Plante, Edith; Cote, Jean-Marc; Gilbert, Marcel; Chahine, Mohamed
CS (1) Quebec Heart Inst., Laval Hosp., Sainte-Foy Canada
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I57.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 19 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:522397 BIOSIS
DN PREV199800522397
TI "Touchdown vectorete-PCR": An efficient method for establishing unknown intronic sequences of ***LQT*** genes.
AU Rubie, C. (1); Schulze-Bahr, E. (1); Myriam, B.; Wedekind, H. (1); Haverkamp, W. (1); Moennig, G. (1); Mergenthaler, J. (1); Borggerefe, M. (1); Assmann, G.; Breithardt, G. (1); Guicheney, P.; Funke, H.
CS (1) Inst. Arteriosclerosis Res., Muenster Germany
SO European Heart Journal, (***Aug., 1998***) Vol. 19, No. ABST. SUPPL., pp. 39.
Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology . ISSN: 0195-668X.
DT Conference
LA English

L9 ANSWER 20 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:333989 BIOSIS
DN PREV199800333989
TI Multiple mechanisms of HERG channel dysfunction in human ***long*** ***QT*** associated mutations.
AU Zhou, Zhengfeng; Gong, Qiuming; Epstein, Miles; January, Craig T.
CS Dep. Anat. Med., Univ. Wis., Madison, WI USA
SO Biophysical Journal, (***Feb., 1998***) Vol. 74, No. 2 PART 2, pp. A26.
Meeting Info.: Forty-second Annual Meeting of the Biophysical Society Kansas City, Missouri, USA February 22-26, 1998
ISSN: 0006-3495.
DT Conference
LA English

L9 ANSWER 21 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:523332 BIOSIS
DN PREV199900523332
TI Mathematical models of cardiac action potentials confirm the ability of SCN5A and ***HERG*** ***mutations*** in congenital ***long*** ***QT*** syndrome to induce early afterdepolarizations.
AU Clausen, Chris (1); Cohen, Ira S. (1); Rosen, Michael R.
CS (1) State Univ. N.Y. Stony Brook, Stony Brook, NY USA
SO Circulation, (***Oct. 27, 1998***) Vol. 98, No. 17 SUPPL., pp. I10-I11.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association . ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 22 OF 53 CAPLUS COPYRIGHT 2002 ACS
AN 1997:447456 CAPLUS
DN 127:79454
TI Molecular bases for ***long*** ***QT*** syndrome
AU Nakajima, Tadashi; Nagai, Ryozo
CS Igakubu, Gunma Daigaku, Maebashi, 371, Japan
SO Igaku no Ayumi (***1997***), 181(10), 906-910
CODEN: IGAYAY; ISSN: 0039-2359
PB Ishiyaku
DT Journal; General Review
LA Japanese
AB A review, with 20 refs., on causative genes (KVLQT1, ***HERG*** , and SCN5A) and ***mutations*** identified by linkage anal. of congenital ***long*** ***QT*** syndrome, Romano-Ward syndrome. The structure and physiol. function of KVLQT1, HERG, and SCN5A are also discussed.

L9 ANSWER 23 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 1997:511503 BIOSIS
DN PREV199799810706
TI Two isoforms of the mouse Ether-a-go-go-related gene coassemble to form channels with properties similar to the rapidly activating component of the cardiac delayed rectifier K+ current.
AU London, Barry (1); Trudeau, Matthew C.; Newton, Kimberly P.; Beyer, Anita K.; Copeland, Neal G.; Gilbert, Debra J.; Jenkins, Nancy A.; Satler, Carol A.; Robertson, Gail A.
CS (1) Div. Cardiol., Univ. Pittsburgh Med. Cent., BST 1744, 200 Lothrop St., Pittsburgh, PA 15213-2582 USA
SO Circulation Research, (1997) Vol. 81, No. 5, pp. 870-878.
ISSN: 0009-7330.
DT Article
LA English
AB HERG, the human ether-a-go-go-related gene, encodes a K+-selective channel with properties similar to the rapidly activating component of the delayed rectifier K+ current (I-Kr). ***Mutations*** of ***HERG*** cause the autosomal-dominant ***long*** - ***QT*** syndrome (LQTS), presumably by disrupting the normal function of I-Kr. The current produced by HERG is not identical to I-Kr, however, and the mechanism by which ***HERG*** ***mutations*** cause LQTS remains uncertain. To better define the role of Erg in the heart, we cloned Merg1 from mouse genomic and cardiac cDNA libraries. Merg1 has 16 exons and maps to mouse chromosome 5 in an area syntenic to human chromosome 7q, the map locus of HERG. We isolated three cardiac isoforms of Merg1: Merg1a is homologous to HERG and is expressed in heart, brain, and testes, Merg1a' lacks the first 59 amino acids of Merg1a and is not expressed abundantly, and Merg1b has a markedly shorter divergent N-terminal cytoplasmic domain and is expressed specifically in the heart. The Merg1 isoforms, like HERG, produce inwardly rectifying E-4031-sensitive currents when heterologously expressed in Xenopus oocytes. Merg1a and HERG produce currents with slow deactivation kinetics, whereas Merg1a+ and Merg1b currents deactivate more rapidly. Merg1b coassembles with Merg1a to form channels with deactivation kinetics that are more rapid than those of Merg1a or HERG and nearly identical to I-Kr. In addition, a homologue of Merg1b is present in human cardiac and smooth muscle. Thus, we have identified a novel N-terminal Erg isoform that is expressed specifically in the heart, has rapid deactivation kinetics, and coassembles with the longer isoform in Xenopus oocytes. This N-terminal Erg isoform may determine the properties of I-Kr and contribute to the pathogenesis of LQTS.

L9 ANSWER 24 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1997:65643 BIOSIS
DN PREV199799364846
TI The human DELTA-1261 ***mutation*** of the ***HERG*** potassium channel results in a truncated protein that contains a subunit interaction domain and decreases the channel expression.
AU Li, Xiaodong; Xu, Jia; Li, Min (1)

CS (1) Dep. Physiol., Johns Hopkins Univ. Sch. Med., 725 N. Wolfe St., WBSB 216, Baltimore, MD 21205 USA
SO Journal of Biological Chemistry, (1997) Vol. 272, No. 2, pp. 705-708.
ISSN: 0021-9258.
DT Article
LA English
AB HERG (human eag-related gene) encodes an inward-rectifier potassium channel formed by the assembly of four subunits. Since the truncated HERG protein in patients with ***long*** ***QT*** syndrome induces a dominant phenotype, that is, cardiac sudden death, the assembly of nonfunctional complexes between wild-type and mutated subunits was implicated in causing the disease. To understand HERG-mediated cardiac sudden death at the molecular level, it is important to determine which regions in the HERG protein participate in subunit interaction. We therefore report the identification of a subunit interaction domain, NAB-HERG, that is localized at the hydrophilic cytoplasmic N terminus and can form a tetramer in the absence of the rest of the HERG protein. Truncated HERG proteins containing NAB-HERG, including one that resulted from the DELTA-1261 human mutation, inhibit the functional expression of the HERG channel in transfected cells. Together, these results support the notion that the expression of HERG in the human heart may be decreased in the presence of the truncated subunit. Such a decrease of potassium channel expression can contribute to the longer QT intervals observed in the patients with the ***HERG*** ***mutation*** .

L9 ANSWER 25 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 12
AN 1997:110483 BIOSIS
DN PREV199799409686
TI Four novel KVLQT1 and four novel ***HERG*** ***mutations*** in familial ***long*** - ***QT*** syndrome.
AU Tanaka, Toshihiro (1); Nagai, Ryozo; Tomoike, Hitonobu; Takata, Shigeo; Yano, Katsusuke; Yabuta, Keijiro; Haneda, Noriyuki; Nakano, Osami; Shibata, Akira; Sawayama, Toshitami; Kasai, Hideaki; Yazaki, Yoshio; Nakamura, Yusuke
CS (1) Lab. Molecular Med., Inst. Med. Sci., Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108 Japan
SO Circulation, (1997) Vol. 95, No. 3, pp. 565-567.
ISSN: 0009-7322.
DT Article
LA English
AB Background. Familial ***long*** - ***QT*** syndrome (LQTS) is characterized by prolonged ventricular repolarization. Clinical symptoms include recurrent syncopal attacks, and sudden death may occur due to ventricular tachyarrhythmias. Three genes responsible for this syndrome (KVLQT1, HERG, and SCN5A) have been identified so far. We investigated mutations of these genes in LQTS families. Methods and Results. Thirty-two Japanese families with LQTS were brought together for screening for mutations. Genomic DNA from each proband was examined by the polymerase chain reaction-single-strand conformation polymorphism technique followed by direct DNA sequencing. In four of the families, comprising 16 patients, mutations were identified in KVLQT1; five other families (9 patients) segregated mutant alleles of HERG. All 25 of these patients carried the specific mutations present in their respective families, and none of 80 normal individuals carried these alleles. Mutations were confirmed by endonuclease digestion or hybridization of mutant allele-specific oligonucleotides. No mutation in SCN5A was found in any family. Conclusions. We identified nine different mutations among 32 families with LQTS. Eight of these were novel and account for 25% of all types of mutations reported to date. Such a variety of mutations makes it difficult to screen high-risk groups using simple methods such as endonuclease digestion or mutant allele-specific amplification.

L9 ANSWER 26 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:424731 BIOSIS
DN PREV199799723934
TI Electrophysiological properties of ***HERG*** ***mutations*** in Japanese LQT2 families.
AU Nakajima, Tadashi (1); Furukawa, Tetsushi; Tanaka, Toshihiro; Nakamura, Yusuke; Nagai, Ryozo; Hiraoka, Masayasu (1)
CS (1) Dep. Cardiovasc Diseases, MRI, Tokyo Med. and Dent. Univ., Tokyo Japan
SO Journal of Molecular and Cellular Cardiology, (1997) Vol. 29, No. 7, pp. A295.
Meeting Info.: XIV Annual Meeting of the International Society for Heart Research Japanese Section Ashikawa, Japan July 18-19, 1997
ISSN: 0022-2828.
DT Conference; Abstract
LA English

L9 ANSWER 27 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 13
AN 1997:511565 BIOSIS
DN PREV199799810768
TI Multi-undulant T-U-wave, sinus bradycardia and ***long*** ***QT*** syndrome: A possible phenotype of mutant genes controlling the inward potassium rectifiers.
AU Shen, Ching-Tsuen (1); Wu, Ying-Chin; Yu, Steven Shih-Tsun; Wang, Nan-Koong
CS (1) Cathay General Hosp., 280, Sect. 4, Jen-Ai Rd., Taipei Taiwan
SO Acta Paediatrica Sinica, (1997) Vol. 38, No. 4, pp. 267-275.
ISSN: 0001-6578.
DT Article
LA English
AB Inward rectifying potassium currents (Ikr and Iks) during phase 3 repolarization of the myocyte from the beginning to the end of repolarization of the myocardial syncytium will inscribe a T-U-wave on the surface electrocardiogram (ECG). Type two congenital ***long*** ***QT*** syndrome (LQT2) is a phenotype of human ether-a-go-go-related gene (***HERG***) ***mutation*** on the chromosome 7q 35-36. Type one congenital ***long*** ***QT*** syndrome (LQT1) is a phenotype of KvLQT1 mutation on the chromosome 11p15.5. Both LQT1 and LQT2 relate with inward rectifying potassium currents and is repolarization related, therefore, it is speculate that patients of LQT1 and LQT2 may have an abnormal T-U-wave on their surface ECG. To two probands of congenital ***LQT*** , 8 patients of structural heart disease treated by open heart surgery, 13 patients of structural heart disease without open-heart surgery, and 10 patients of normal controls, 24 hour-Holter monitoring was performed from July to December 1996. Their corrected QT interval (QTc) as well as the RR interval of every heart beat was calculated by a computer. The results showed that all 33 patients exhibited beat-by-beat fluctuation of their QTc and RR daily. The RR intervals of these two probands of congenital ***LQT*** were somewhile more than 1200 ms during circadian waking time, while 31 cases without ***LQT*** showed their RR prolongation only during the circadian sleeping time. A multi-undulant T-U-wave, or a beat-to-beat changing of vectors or amplitudes of their T-U-wave observed in these two probands of congenital ***LQT*** , were not observable in those 31 patients without congenital ***LQT*** . Therefore, we concluded that multi-undulant T-U-wave, sinus bradycardia and a longer QTc was a phenotype of the mutated genes which control the inward rectifying potassium currents during phase 3 repolarization.

L9 ANSWER 28 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:16352 BIOSIS
DN PREV199800016352
TI Molecular epidemiology of the ***Long*** ***QT*** syndrome.
AU Priori, Silvia G. (1); Napolitano, Carlo; Schwartz, Peter J. (1); Paganini, Vincenzo (1); Casari, Giorgio
CS (1) Policlin. S. Matteo, Pavia Italy
SO Circulation, (***10/21/97, 1997***) Vol. 96, No. 8 SUPPL., pp. I212.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 29 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:16351 BIOSIS
DN PREV199800016351
TI Identification of a ***mutational*** hot spot in ***HERG*** -related ***Long*** ***QT*** syndrome (LQT2): Phenotypic implications.
AU Napolitano, Carlo (1); Priori, Silvia G.; Schwartz, Peter J.; Timothy, Katherine; Paganini, Vincenzo; Cantu, Francesco; Bloisi, Raffaella; De Fusco, Maurizio; Spazzolini, Carla; Casari, Giorgio
CS (1) Osp. Civile, Milan Italy
SO Circulation, (***10/21/97, 1997***) Vol. 96, No. 8 SUPPL., pp. I212.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 30 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:72728 BIOSIS
DN PREV199800072728
TI Molecular physiology of cardiac delayed rectifier K+ channels.
AU Sanguinetti, Michael C. (1); Zou, Anruo
CS (1) Univ. Utah, Dep. Med., Div. Cardiol., Build. 533, Room 4220, Salt Lake City, UT 84112 USA
SO Heart and Vessels, (1997) Vol. 0, No. SUPPL. 12, pp. 170-172.
ISSN: 0910-8327.
DT Article
LA English
AB Delayed rectifier K+ current in cardiac myocytes is the sum of two distinct currents, IKr and IKs. The molecular basis of these channels has recently been defined. HERG subunits coassemble to form IKr channels. KvLQT1 and minK subunits coassemble to form IKs channels. ***Mutations*** in ***HERG*** or KVLQT1 genes predispose affected individuals to ventricular arrhythmias and sudden death.

L9 ANSWER 31 OF 53 CAPLUS COPYRIGHT 2002 ACS
AN 1997:185322 CAPLUS
DN 126:275543
TI Molecular bases for ***long*** ***QT*** syndrome (***LQT***): mutations in cardiac ion channel genes cause ***LQT***
AU Nakajima, Tadashi; Keneko, Yoshiaki; Nagai, Kaneko
CS Dep. Internal Med. II, Gunma Univ. Sch. Med., Japan
SO Kokyu to Junkan (***1997***), 45(2), 121-128
CODEN: KOJUA9; ISSN: 0452-3458

PB Igaku Shoin
DT Journal; General Review
LA Japanese
AB A review with 22 refs., on the theory of inherited ***Long*** ***QT*** syndrome, and genetic factors and abnormal ion channels (i.e. KVLQT1, HERG, and SCN5A) in Romano-Ward syndrome.

L9 ANSWER 32 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:15483 BIOSIS
DN PREV199800015483
TI Complete analysis of the ***HERG*** gene for ***mutations*** in ***long*** ***QT*** syndrome.
AU Vesely, Mark R. (1); Duggal, Priya (1); London, Barry; Wattanasirichaigoon, Duangrurdee (1); Beggs, Alan H. (1)
CS (1) Children's Hosp., Boston, MA USA
SO Circulation, (***10/21/97, 1997***) Vol. 96, No. 8 SUPPL., pp. I56.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 33 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 1997:19310 BIOSIS
DN PREV199799318513
TI Molecular physiology and pharmacology of HERG: Single-channel currents and block by dofetilide.
AU Kiehn, Johann; Lacerda, Antonio E.; Wible, Barbara; Brown, Arthur M. (1)
CS (1) Rammelkamp Cent., 2500 MetroHealth Dr., Cleveland, OH 44109-1998 USA
SO Circulation, (1996) Vol. 94, No. 10, pp. 2572-2579.
ISSN: 0009-7322.
DT Article
LA English
AB Background: The human ether-a-go-go-related gene (HERG) is one locus for the hereditary ***long*** - ***QT*** syndrome. A hypothesis is that HERG produces the repolarizing cardiac potassium current I-Kr, with the consequence that ***mutations*** in ***HERG*** prolong the QT interval by reducing I-Kr. The elementary properties of HERG are unknown, and as a test of the hypothesis that HERG produces I-Kr, we compared their elementary properties. Methods and Results: We injected HERG cRNA into Xenopus oocytes and measured currents from single channels or current variance from the noise produced by ensembles of channels recorded from macro patches. Single-channel conductance was dependent on the extracellular potassium concentration ((K)-o). At physiological (K)-o, it was 2 picosiemens (pS), and at 100 mmol/L (K)-o, it was 10 pS. Openings occurred in bursts with a mean duration of 26 ms at - 100 mV. Mean open time was 3.2 ms and closed times were 1.0 and 26 ms. In excised macro patches, HERG currents were blocked by the class III antiarrhythmic drug dofetilide, with an IC-50 of 35 nmol/L. Dofetilide block was slow and greatly attenuated at positive potentials at which HERG rectifies. Conclusions: The microscopic physiology of HERG and I-Kr is similar, consistent with HERG being an important component of I-Kr. The pharmacology is also similar; dofetilide appears to primarily block activated channels and has a much lower affinity for closed and inactivated channels.

L9 ANSWER 34 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
15
AN 1996:183369 BIOSIS
DN PREV199698739498
TI Spectrum of HERG K+-channel dysfunction in an inherited cardiac arrhythmia.
AU Sanguinetti, Michael C. (1); Curran, Mark E.; Spector, Peter S.; Keating, Mark T.
CS (1) Eccels Program Human Mol. Biol. Genetics, University Utah Health Sci. Center, Salt Lake City, UT 84112 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (1996) Vol. 93, No. 5, pp. 2208-2212.
ISSN: 0027-8424.
DT Article
LA English
AB ***Long*** ***QT*** syndrome (***LQT***) is an autosomal dominant disorder that can cause sudden death from cardiac arrhythmias. We recently discovered that ***mutations*** in ***HERG*** , a K+-channel gene, cause chromosome 7-linked ***LQT*** . Heterologous expression of HERG in Xenopus oocytes revealed that HERG current was similar to a well-characterized cardiac delayed rectifier K+ current, I-Kr, and led to the hypothesis that ***mutations*** in ***HERG*** reduced I-Kr, causing prolonged myocellular action potentials. To define the mechanism of ***LQT*** , we injected oocytes with mutant HERG complementary RNAs, either singly or in combination with wild-type complementary RNA. Some mutations caused loss of function, whereas others caused dominant negative suppression of ***HERG*** function. These ***mutations*** are predicted to cause a spectrum of diminished I-Kr and delayed ventricular repolarization, consistent with the prolonged QT interval observed in individuals with ***LQT*** .

L9 ANSWER 35 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16
AN 1996:520741 BIOSIS
DN PREV199699243097
TI Multiple mechanisms in the ***long*** - ***QT*** syndrome: Current knowledge, gaps and future directions.
AU Roden, Dan M.; Lazzara, Ralph; Rosen, Michael; Schwartz, Peter J.; Towbin, Jeffry; Vincent, Michael
CS Dep. Med., LDS Hosp., Eight Ave. and C St., Salt Lake City, UT 84143-0001 USA
SO Circulation, (1996) Vol. 94, No. 8, pp. 1996-2012.
ISSN: 0009-7322.
DT General Review
LA English
AB The congenital ***long*** - ***QT*** syndrome (LQTS) is characterized by prolonged QT intervals, QT interval lability, and polymorphic ventricular tachycardia. The manifestations of the disease vary, with a high incidence of sudden death in some affected families but not in others. Mutations causing LQTS have been identified in three genes, each encoding a cardiac ion channel. In families linked to chromosome 3, mutations in SCN5A, the gene encoding the human cardiac sodium channel, cause the disease. Mutations in the human ether-a-go-go-related gene (HERG), which encodes a delayed-rectifier potassium channel, cause the disease in families linked to chromosome 7. Among affected individuals in families linked to chromosome 11, mutations have been identified in KVLQT1, a newly cloned gene that appears to encode a potassium channel. The SCN5A mutations result in defective sodium channel inactivation, whereas ***HERG*** ***mutations*** result in decreased outward potassium current. Either mutation would decrease net outward current during repolarization and would thereby account for prolonged QT intervals on the surface ECG. Preliminary data suggest that the clinical presentation in LQTS may be determined in part by the gene affected and possibly even by the specific mutation. The identification of disease genes in LQTS not only represents a major milestone in understanding the mechanisms underlying this disease but also presents new opportunities for combined research at the molecular, cellular, and clinical levels to understand issues such as adrenergic regulation of cardiac electrophysiology and mechanisms of susceptibility to arrhythmias in LQTS and other settings.

L9 ANSWER 36 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
17
AN 1996:263817 BIOSIS
DN PREV199698819946
TI Missense mutation in the pore region of HERG causes familial ***long*** ***QT*** syndrome.
AU Benson, D. Woodrow; Macrae, Calum A.; Vesely, Mark R.; Walsh, Edward P.; Seidman, J. G.; Seidman, Christine E.; Satler, Carol Ann (1)
CS (1) Children's Hosp., Dep. Cardiol., 300 Longwood Ave., Enders 13, Boston, MA 02115 USA
SO Circulation, (1996) Vol. 93, No. 10, pp. 1791-1795.
ISSN: 0009-7322.
DT Article
LA English
AB Background: ***Long*** ***QT*** syndrome (***LQT***) is an inherited cardiac disorder that results in syncope, seizures, and sudden death. In a family with ***LQT*** , we identified a novel mutation in human ether-a-go-go-related gene (HERG), a voltage-gated potassium channel. Methods and Results: We used DNA sequence analysis, restriction enzyme digestion analysis, and allele-specific oligonucleotide hybridization to identify the ***HERG*** ***mutation*** . A single nucleotide substitution of thymidine to guanine (T1961G) changed the coding sense of HERG from isoleucine to arginine (Ile593Arg) in the channel pore region. The mutation was present in all affected family members; the mutation was not present in unaffected family members or in 100 normal, unrelated individuals. Conclusions: We conclude that the Ile593Arg missense ***mutation*** in ***HERG*** is the cause of ***LQT*** in this family because it segregates with disease, its presence was confirmed in three ways, and it is not found in normal individuals. The Ile593Arg mutation may result in a change in potassium selectivity and permeability leading to a loss of HERG function, thereby resulting in ***LQT*** .

L9 ANSWER 37 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
18
AN 1996:484439 BIOSIS
DN PREV199699199695
TI A ***mutation*** in ***HERG*** associated with notched T waves in ***long*** ***QT*** syndrome.
AU Dausse, Eric; Berthet, Myriam; Denjoy, Isabelle; Andre-Fouet, Xavier; Cruaud, Corrine; Bennaceur, Mohammed; Faure, Sabien; Coumel, Philippe; Schwartz, Ketty; Guicheney, Pascale (1)
CS (1) INSERM UR 153, Hopital Pitie-Salpetriere, Inst. de Myologie, 47 Boulevard de l'Hopital, 75013 France
SO Journal of Molecular and Cellular Cardiology, (1996) Vol. 28, No. 8, pp. 1609-1615.
ISSN: 0022-2828.
DT Article
LA English
AB ***Long*** ***QT*** syndrome (***LQT***) is a genetically

heterogeneous inherited disorder that causes sudden death from cardiac arrhythmia. Four loci have been mapped to chromosomes 3, 4, 7 and 11 and three specific mutated genes for ***LQT*** syndrome have been identified. LQT2 results from mutations in the human ether-a-gogo-related gene, HERG, a cardiac potassium channel, whose protein product likely underlies I-Kr, the rapidly activating delayed rectifier current. By SSCP analysis and direct sequencing, we determined a new missense ***mutation*** in the ***HERG*** coding sequence, a G to A transition at position 1681 resulting in the substitution of threonine for a highly conserved alanine at codon 561. This mutation, Ala561Thr, in the coding sequence of the fifth membrane-spanning domain (S5) of the HERG protein seems to convey a risk of cardiac events in affected family members. In addition to a prolonged T wave of low amplitude on the surface ECG, a distinctive biphasic T-wave pattern was found in the left precordial leads of all affected subjects with the Ala561Thr mutation regardless of age, gender and beta blocking therapy.

L9 ANSWER 38 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
19
AN 1996:458253 BIOSIS
DN PREV199699180609
TI Genetically defined therapy of inherited ***long*** - ***QT*** syndrome: Correction of abnormal repolarization by potassium.
AU Compton, Steve J.; Lux, Robert L.; Ramsey, Matthew R.; Strelich, Katie R.; Sanguinetti, Michael C.; Green, Larry S.; Keating, Mark T.; Mason, Jay W. (1)
CS (1) Div. Cardiol. 4A-100 Univ. Utah Health Sci. Cent., Salt Lake City, UT 84132-0001 USA
SO Circulation, (1996) Vol. 94, No. 5, pp. 1018-1022.
ISSN: 0009-7322.
DT Article
LA English
AB Background: Many members of families with inherited ***long*** - ***QT*** (***LQT***) syndrome have ***mutations*** in ***HERG*** , a gene encoding a cardiac potassium channel that is modulated by extracellular potassium. We hypothesized that an increase in serum potassium would normalize repolarization in these patients. Methods and Results: We studied seven subjects with chromosome 7-linked ***LQT*** syndrome and five normal control subjects. Repolarization was measured by ECG and body surface potential mapping during sinus rhythm, exercise, and atrial pacing, before and after serum potassium increase. Potassium administration improved repolarization in the ***LQT*** syndrome. At baseline, ***LQT*** subjects differed from control subjects: resting corrected QT interval (QT-c, 627+-90 versus 425+-25 ms, P=.0007), QT, dispersion (133+-62 versus 36+-9 ms. P=.009), QT/RR slope (0.35+-0.08 versus 0.24+-0.07, P=.04). and global root-mean-square QT interval (RMS-QT-c; 525+-68 versus 393+-22, P=.002). All ***LQT*** subjects had biphasic or notched T waves. After administration of potassium, the ***LQT*** group had a 24% reduction in resting QT-c interval (from 617+-92 to 469+-23 ms, P=.004) compared with a 4% reduction among control subjects (from 425+-25 to 410+-45 ms. P gt .05). The reduction was significantly greater in ***LQT*** subjects (P=.018). QT dispersion became normal in ***LQT*** subjects and did not change in control subjects. The slope of the relation between QT interval and cycle length (QT/RR slope) decreased toward normal. T-wave morphology improved in six of seven ***LQT*** subjects. The ***LQT*** group had a greater reduction in RMS-QT-c than control subjects (P=.04). Conclusions: An increase in serum potassium corrects abnormalities of repolarization duration, T-wave morphology, QT/RR slope, and QT dispersion in patients with chromosome 7-linked ***LQT*** .

L9 ANSWER 39 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
20
AN 1996:332645 BIOSIS
DN PREV199699055001
TI High affinity open channel block by dofetilide of HERG expressed in a human cell line.
AU Snyders, Dirk J.; Chaudhary, Archana
CS Dep. Med., 554-MRB2, Vanderbilt Univ. Sch. Med., Nashville, TN 37232-6602 USA
SO Molecular Pharmacology, (1996) Vol. 49, No. 6, pp. 949-955.
ISSN: 0026-895X.
DT Article
LA English
AB In the ***long*** ***QT*** syndrome, excessive prolongation of the cardiac action potential leads to polymorphic ventricular tachycardia (torsades de pointes) and sudden death. ***Mutations*** in ***HERG*** have been identified as one of the causes of the chromosome 7-linked form of congenital ***long*** ***QT*** syndrome. The biophysical properties of currents recorded from HERG expressing Xenopus oocytes are similar to those of a cardiac K+ current, I-Kr, but the characteristic nanomolar methanesulfonanilide sensitivity has not been demonstrated. To determine the biophysical and pharmacological properties of HERG under experimental conditions similar to those used to study native cardiac currents, we examined currents expressed after expression of HERG in a human cell line, human embryonic kidney 293. Transfected cells displayed K+-selective outward currents that activated at membrane potentials positive to -50 mV with strongly voltage-dependent kinetics (time constant (tau) = 2 sec at -20 mV and 188 msec at +20 mV). Marked inward rectification was observed for depolarizations positive to +0 mV, which was due to rapid channel inactivation (tau = 6 msec at +50 mV). The subsequent tail currents at -40 mV displayed an initial rising phase with tau = 10 msec, followed by a slow multiexponential decline. The EC-50 for the methanesulfonanilide I-Kr blocker dofetilide was 12 +- 2 nM. Induction of block depended on depolarization beyond the threshold for channel opening. Time-dependent block developed slowly, with tau = 5.2 +- 0.6 sec (300 nM) at + 10 mV, and was delayed by stronger depolarizations. This pattern suggested that dofetilide preferentially blocks open (or activated) channels and that the fast inactivation may competitively slow the binding kinetics. The latter occurrence was further supported by a simplified mathematical model that addressed the impact on binding kinetics of fast inactivation. These results indicate that the HERG gene product encodes an alpha subunit that, when expressed in mammalian cells, displays both the major functional and pharmacological properties of native I-Kr. Dofetilide acts as a slow-onset/slow-offset open channel blocker of this current at nanomolar concentrations.

L9 ANSWER 40 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:6249 BIOSIS
DN PREV199799305452
TI Frequency and phenotype of ***HERG*** ***mutations*** in congenital ***long*** ***QT*** syndrome (LQTS.
AU Schulze-Bahr, Eric (1); Haverkamp, Wilhelm; Wiebusch, Heiko; Wedekind, Horst; Hordt, Marco; Borggrefe, Martin; Breithardt, Gunter; Funke, Harald
CS (1) Muenster Univ., Muenster Germany
SO Circulation, (1996) Vol. 94, No. 8 SUPPL., pp. I719.
Meeting Info.: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322.
DT Conference; Abstract
LA English

L9 ANSWER 41 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
21
AN 1996:160519 BIOSIS
DN PREV199698732654
TI Class III antiarrhythmic drugs block HERG, a human cardiac delayed rectifier K+ channel: Open-channel block by methanesulfonanilides.
AU Spector, Peter S.; Curran, Mark E.; Keating, Mark T.; Sanguinetti, Michael C. (1)
CS (1) Cardiol. Div., Univ. Utah Health Sci. Cent., Salt Lake City, UT 84112 USA
SO Circulation Research, (1996) Vol. 78, No. 3, pp. 499-503.
ISSN: 0009-7330.
DT Article
LA English
AB We recently reported that ***mutations*** in ***HERG*** , a potassium channel gene, cause ***long*** ***QT*** syndrome. Heterologous expression of HERG in Xenopus oocytes revealed that this channel had biophysical properties nearly identical to a cardiac delayed rectifier K+ current, I-Kr, but had dissimilar pharmacological properties. Class III antiarrhythmic drugs such as E-4031 and MK-499 are potent and specific blockers of I-Kr in cardiac myocytes. Our initial studies indicated that these compounds did not block HERG at a concentration of 1 mu-mol/L. In the present study, we used standard two-microelectrode voltage-clamp techniques to further characterize the effects of these drugs on HERG channels expressed in oocytes. Consistent with initial findings, 1 mu-mol/L MK-499 and E-4031 had no effect on HERG when oocytes were voltage clamped at a negative potential and not pulsed during equilibration with the drug. However, MK-499 did block HERG current if oocytes were repetitively pulsed, or clamped at a voltage positive to the threshold potential for channel activation. This finding is in contrast to previous studies that showed significant block of I-Kr in isolated myocytes by similar drugs, even in the absence of pulsing. This apparent discrepancy may be due to differences in channel characteristics (HERG versus guinea pig and mouse I-Kr), tissue (oocytes versus myocytes), or specific drugs. Under steady state conditions, block of HERG by MK-499 was half maximal at 123 +- 12 nmol/L at a test potential of -20 mV. MK-499 (150 nmol/L) did not affect the voltage dependence of activation and rectification nor the kinetics of activation and deactivation of HERG. These data indicate that MK-499 preferentially blocks open HERG channels and further support the conclusion that HERG subunits form I-Kr channels in cardiac myocytes.

L9 ANSWER 42 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:93901 BIOSIS
DN PREV199799393104
TI Genetic analysis of familial ***long*** ***QT*** syndrome: Missense ***mutation*** in ***HERG*** in LQT2 family.
AU Akimoto, Kaoru (1); Kasanuki, Hiroshi; Furutani, Michiko; Imamura, Shin-Ichiro; Furutani, Yoshiynki; Takao, Atsuyoshi; Momma, Kazuo; Matsuoka, Rumiko
CS (1) Dep. Pediatrics, Miyakonojo Med. Association Hosp., Miyakonojo Japan
SO Japanese Circulation Journal, (1996) Vol. 60, No. 7, pp. 447.
Meeting Info.: 60th Annual Scientific Meeting of the Japanese Circulation Society Osaka, Japan March 19-21, 1996
ISSN: 0047-1828.
DT Conference; Abstract
LA English

L9 ANSWER 43 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:3001 BIOSIS
DN PREV199799302204
TI Coexistence of missense ***mutation*** of ***HERG*** and mitochondrial DNA in Japanese ***long*** ***QT*** family.
AU Akimoto, Kaoru; Furutani, Michiko; Kasanuki, Hiroshi; Imammura, Shin-Ichiro; Furutani, Yoshiyuki; Takao, Atsuyoshi; Momma, Kazuo; Matsuoka, Rumiko
CS Tokoyo Women's Med. Coll., Tokyo Japan
SO Circulation, (1996) Vol. 94, No. 8 SUPPL., pp. I164.
Meeting Info.: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322.
DT Conference; Abstract
LA English

L9 ANSWER 44 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:559900 BIOSIS
DN PREV199699282256
TI A ***mutational*** hotspot in ***HERG*** associated with a severe form of ***long*** ***QT*** syndrome and notched T-waves.
AU Denjoy, I. (1); Dausse, E.; Berthet, M.; Andre-Fouet, X.; Bennacear, M.; Schwartz, K.; Coumel, P. (1); Guicheney, P.
CS (1) Cardiol., Lariboisiere Hosp., Lyon France
SO European Heart Journal, (1996) Vol. 17, No. ABSTR. SUPPL., pp. 125.
Meeting Info.: XVIIIth Congress of the European Society of Cardiology Birmingham, England, UK August 25-29, 1996
ISSN: 0195-668X.
DT Conference
LA English

L9 ANSWER 45 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:355776 BIOSIS
DN PREV199699078132
TI Novel ***mutations*** in ***HERG*** , the human eag-related gene, in ***long*** ***QT*** syndrome (LQTS) supports its role as the LQTS 2-gene.
AU Schulze-Bahr, Eric (1); Haverkamp, Wilhelm (1); Wiebusch, Heiko; Hoerdt, Marko (1); Borggrefe, Martin (1); Assmann, Gerd; Breithardt, Guenter; Funke, Harald
CS (1) Dep. Cardiol. Angiol., Hosp. Univ. Muenster, Muenster Germany
SO European Journal of Human Genetics, (1996) Vol. 4, No. SUPPL. 1, pp. 124.
Meeting Info.: 28th Annual Meeting of the European Society of Human Genetics London, England, UK April 11-13, 1996
ISSN: 1018-4813.
DT Conference
LA English

L9 ANSWER 46 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:555574 BIOSIS
DN PREV199699277930
TI ***HERG*** ***mutations*** are a frequent, but not a major cause for congenital ***long*** - ***QT*** syndrome (LQTS) in the Caucasian population.
AU Schulze-Bahr, E. (1); Haverkamp, W.; Wiebusch, H.; Wedekind, H. (1); Hoerdt, M. (1); Borggrefe, M. (1); Breithardt, G. (1); Assmann, G.; Funke, H.
CS (1) Hosp. Univ. Muenster, Dep. Cardiol. Angiol., Muenster Germany
SO American Journal of Human Genetics, (1996) Vol. 59, No. 4 SUPPL., pp. A108.
Meeting Info.: 46th Annual Meeting of the American Society of Human Genetics San Francisco, California, USA October 29-November 2, 1996
ISSN: 0002-9297.
DT Conference
LA English

L9 ANSWER 47 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:559788 BIOSIS
DN PREV199699282144
TI ***HERG*** ***mutations*** account for approximately 15 percent of patients with congenital ***long*** ***QT*** syndrome.
AU Schulze-Bahr, E. (1); Haverkamp, W. (1); Wiebusch, H.; Borggrefe, M. (1); Hoerdt, M. (1); Briethardt, G. (1); Assmann, G.; Funke, H.
CS (1) Dep. Cardiology, Inst. Arteriosclerosis Res., Univ. Muenster Germany
SO European Heart Journal, (1996) Vol. 17, No. ABSTR. SUPPL., pp. 97.
Meeting Info.: XVIIIth Congress of the European Society of Cardiology Birmingham, England, UK August 25-29, 1996
ISSN: 0195-668X.
DT Conference
LA English

L9 ANSWER 48 OF 53 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96074248 EMBASE
DN 1996074248
TI Mechanisms and management of congenital and acquired ***long*** ***QT*** syndromes.
AU Lazzara R.
CS Cardiovascular Section, University of Oklahoma, Health Sciences Center, 920 Stanton L. Young,Oklahoma City, OK 73104, United States
SO Archives des Maladies du Coeur et des Vaisseaux, (1996) 89/SPEC. ISSUE I (51-55).
ISSN: 0003-9683 CODEN: AMCVAN
CY France
DT Journal; Conference Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English; French
AB The ***long*** ***QT*** syndromes can be divided into congenital and acquired forms. Early afterdepolarizations have been identified as triggering mechanisms for both congenital and acquired QT syndromes but reentry may play a role in the perpetuation of the ventricular tachycardia, torsade de pointes. Studies of the ionic mechanisms of early afterdepolarizations have implicated L-type Ca2+ current, persisting Na+ current, and Na+:Ca2+ exchange current related to Ca2+ loading. Different ionic mechanisms may be operative in early afterdepolarizations occuring at different levels of membrane potential in the setting of prolonged repolarization by blocking K+ currents or maintaining non-inactivating Ca2+ or Na+ currents or in early afterdepolarizations due to adrenergic stimulation. In the congenital ***long*** ***QT*** syndromes, two mutations have recently been discovered in the genes SCN5A and HERG which encode respectively the Na+ channel and a K+ channel conducting the current I(kr). It is postulated that the SCN5A mutation leads to a problem with inactivation of Na+ current. In the case of the ***HERG*** ***mutation*** , the K+ current appears to be diminished. In the case of the acquired ***long*** ***QT*** syndromes, the therapeutic challenge is to maintain the prolonged repolarization but to interrupt the arrhythmogenic cascade. Current therapies for torsades de pointes include speeding of the heart rate, which enhances K+ current, and Ca2+ blockers or Mg, also a Ca2+ blocker. In the congenital ***long*** ***QT*** syndromes, therapy in the past has been directed toward reducting adrenergic influence either by betablockade or left cardiac sympathectomy. Recent discoveries open other possibilities such as Na+ channel blockers and methods to increase I(kr) such as elevation of extracellular K+.

L9 ANSWER 49 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 22
AN 1995:202875 BIOSIS
DN PREV199598217175
TI A molecular basis for cardiac arrhythmia: ***HERG*** ***mutations*** cause ***long*** ***QT*** syndrome.
AU Curran, Mark E. (1); Splawski, Igor (1); Timothy, Katherine W.; Vincent, G. Michael; Green, Eric D.; Keating, Mark T. (1)
CS (1) Dep. Human Genetics, Eccles Program in Human Mol. Biol. Genet., Univ. Utah Health Sci. Center, Salt Lake City, UT 84112 USA
SO Cell, (1995) Vol. 80, No. 5, pp. 795-803.
ISSN: 0092-8674.
DT Article
LA English
AB To identify genes Involved in cardiac arrhythmia, we investigated patients with ***long*** ***QT*** syndrome (LOT), an inherited disorder causing sudden death from a ventricular tachyarrhythmia, torsade de pointes. We previously mapped LOT loci on chromosomes 11 (LQT1), 7 (LQT2), and 3 (LQT3). Here, linkage and physical mapping place LQT2 and a putative potassium channel gene, HERG, on chromosome 7q35-36. Single strand conformation polymorphism and DNA sequence analyses reveal ***HERG*** ***mutations*** in six LOT families, including two intragenic deletions, one splice-donor mutation, and three missense mutations. In one kindred, the mutation arose de novo. Northern blot analyses show that HERG is strongly expressed in the heart. These data indicate that HERG is LQT2 and suggest a likely cellular mechanism for torsade de pointes.

L9 ANSWER 50 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 23
AN 1995:294853 BIOSIS
DN PREV199598309153
TI A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I-Kr potassium channel.
AU Sanguinetti, Michael C.; Jiang, Changan; Curran, Mark E. (1)
CS (1) Eccles Program Human Molecular Biol. Genetics, Univ. Utah Health Sci. Center, Salt Lake City, UT 84112 USA
SO Cell, (1995) Vol. 81, No. 2, pp. 299-307.
ISSN: 0092-8674.
DT Article
LA English
AB ***Mutations*** in ***HERG*** cause an inherited cardiac arrhythmia, ***long*** ***QT*** syndrome (***LQT***). To define the function of HERG, we expressed the protein in Xenopus oocytes. The biophysical properties of expressed HERG are nearly identical to the rapidly activating delayed rectifier K+ current (I-Kr) in cardiac myocytes. HERG current is K+ selective, declines with depolarizations above 0 mV, is activated by extracellular K+, and is blocked by lanthanum. Interestingly, HERG current is not blocked by drugs that specifically block I-Kr in cardiac myocytes. These data indicate that HERG proteins form I-Kr channels, but that an additional subunit may be required for drug sensitivity. Since block of I-Kr is a known mechanism for drug-induced cardiac arrhythmias, the finding that HERG encodes I-Kr channels provides a mechanistic link between certain forms of inherited

and acquired ***LQT*** .

L9 ANSWER 51 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:11649 BIOSIS
DN PREV199698583784
TI Absence of ***HERG*** and SCN5A ***mutations*** in acquired ***long*** ***QT*** syndrome.
AU Wei, Jian; Warhen, Mark; Murray, Katherine; Daw, Richard; Roden, Dan; George, Alfred L., Jr.
CS Vanderbilt Univ., Nashville, TN USA
SO Circulation, (1995) Vol. 92, No. 8 SUPPL., pp. 1275.
Meeting Info.: 68th Scientific Session of the American Heart Association Anaheim, California, USA November 13-16, 1995
ISSN: 0009-7322.
DT Conference
LA English

L9 ANSWER 52 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 24
AN 1995:392157 BIOSIS
DN PREV199598406457
TI Genetic approaches to cardiovascular disease: Supravalvular aortic stenosis, Williams syndrome, and ***long*** - ***QT*** syndrome.
AU Keating, Mark T.
CS Eccles Inst. Hum. Genet., Univ. Utah, Build. 533, Room 2100, Salt Lake City, UT 84112 USA
SO Circulation, (1995) Vol. 92, No. 1, pp. 142-147.
ISSN: 0009-7322.
DT Article
LA English
AB Background: Although family history can be an important risk factor for cardiovascular disease, relatively little is known about the nature of specific genetic risk factors. One approach to this problem is to identify and characterize genes responsible for inherited disorders in the hope that this information will also provide mechanistic insight into common forms of cardiovascular disease. Methods and Results: Over the last decade, it has become possible to identify genes that cause human disease by use of the techniques of molecular genetics, specifically genetic linkage analysis, positional cloning, and mutational analyses. We have used these techniques to study three inherited cardiovascular disorders: supravalvular aortic stenosis, Williams syndrome, and ***long*** - ***QT*** syndrome. We have discovered that the vascular pathology of supravalvular aortic stenosis and Williams syndrome results from mutations involving the elastin gene on chromosome 7q11.23. These mutations include intragenic deletions, translocations, and complete deletion of the elastin gene, suggesting that a quantitative reduction in elastin during vascular development is pathogenically important. To date, only the elastin gene has proved important for supravalvular aortic stenosis. By contrast, genetic linkage analyses in families with ***long*** - ***QT*** syndrome indicate that at least four distinct genes can cause this disorder. We have identified three ***LQT*** loci: LQT1 on chromosome 11p15.5, LQT2 on 7q35-36, and LQT3 on 3p21-24. Recently, we demonstrated that mutations in a putative cardiac potassium channel gene, HERG, are responsible for the chromosome 7-linked form of ***long*** - ***QT*** syndrome, whereas mutations in the cardiac sodium channel gene SCN5A cause the chromosome 3-linked form of this disorder. ***HERG*** ***mutations*** and potassium channel biophysics suggest a dominant-negative molecular mechanism and reduced repolarization currents. By contrast, SCN5A mutations probably cause subtle alterations of cardiac sodium channel function and prolonged depolarizing currents. Conclusions: Molecular genetic analyses of ***long*** - ***QT*** syndrome, supravalvular aortic stenosis, and Williams syndrome have begun to unravel the mechanisms underlying these inherited disorders. Rapid genetic testing for Williams syndrome is now available using a simple cytogenetic test, fluorescence in situ hybridization, but additional work will be required for ***long*** - ***QT*** syndrome and autosomal-dominant supravalvular aortic stenosis. Improved diagnosis and mechanistic understanding of these disorders should lead to rational treatment and prevention.

L9 ANSWER 53 OF 53 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 25
AN 1995:388492 BIOSIS
DN PREV199598402792
TI HERG, a human inward rectifier in the voltage-gated potassium channel family.
AU Trudeau, Matthew C.; Warmke, Jeffrey W.; Ganetzky, Barry; Robertson, Gail A. (1)
CS (1) Dep. Physiol., Univ. Wis. Med. Sch., 1300 University Ave., Madison, WI 53706 USA
SO Science (Washington D C), (1995) Vol. 269, No. 5220, pp. 92-95.
ISSN: 0036-8075.
DT Article
LA English
AB In contrast to other members of the Eag family of voltage-gated, outwardly rectifying potassium channels, the human eag-related gene (HERG) has now been shown to encode an inwardly rectifying potassium channel. The properties of HERG channels are consistent with the gating properties of Eag-related and other outwardly rectifying, S4-containing potassium channels, but with the addition of an inactivation mechanism that attenuates potassium efflux during depolarization. Because ***mutations*** in ***HERG*** cause a form of ***long*** - ***QT*** syndrome, these properties of HERG channel function may be critical to the maintenance of normal cardiac rhythmicity.

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NEWS 7 Mar 22 TOXLIT no longer available
NEWS 8 Mar 22 TRCTHERMO no longer available
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NEWS 17 Apr 22 BIOSIS Gene Names now available in TOXCENTER
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L1 2057209 POTASSIUM OR K

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L2 2176141 BLOCKER? OR ACTIVAT?

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=> s potassium channel? or K channel?
L3 68771 POTASSIUM CHANNEL? OR K CHANNEL?

=> s l3 (3a) l2
L4 21927 L3 (3A) L2

=> s l4 and drug sreen?
L5 0 L4 AND DRUG SREEN?

=> s l4 and py<1998
1 FILES SEARCHED...
L6 14252 L4 AND PY<1998

=> s l6 and voltage
L7 4283 L6 AND VOLTAGE

=> d bib abs 1-5

L7 ANSWER 1 OF 4283 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:507129 BIOSIS
DN PREV199800507129
TI Role of K+ channels in EDHF-dependent relaxation induced by acetylcholine in canine coronary artery.
AU Nakashima, Yoshihito; Toko, Yukio; Fukami, Yasumasa; Hibino, Michitaka; Okumura, Kenji; Ito, Takayuki (1)
CS (1) Intern. Med. 2, Nagoya Univ. Sch. Med., 65 Turumai-cho, Showa-ku, Nagoya 466 Japan
SO Heart and Vessels, (1997) Vol. 12, No. 6, pp. 287-293.
ISSN: 0910-8327.
DT Article
LA English
AB To identify the K+ channels responsible for endothelium-derived hyperpolarizing factor (EDHF)-dependent relaxation, we studied the effects of various ***K*** + ***channel*** ***blockers*** on acetylcholine-induced relaxation, which persists even in the presence of both an inhibitor of nitric oxide synthase and that of cyclooxygenase, in canine coronary artery rings. A nonselective ***K*** + ***channel*** ***blocker*** , tetrabutylammonium (TBA), a large and intermediate conductance Ca2+- ***activated*** ***K*** + ***channel*** ***blocker*** , charybdotoxin (CTX), and a ***voltage*** -dependent ***K*** + ***channel*** ***blocker*** , 4-aminopyridine (4-AP), significantly inhibited this residual relaxation. A combined treatment with CTX and 4-AP almost completely blocked the relaxation. Neither a large (iberiotoxin) nor a small (apamin) conductance Ca2+- ***activated*** ***K*** + ***channel*** ***blocker*** blocked the relaxation. We also investigated effects of ***K*** + ***channel*** ***blockers*** on basal tone to determine whether or not EDHF is involved in regulating basal tone. TBA and CTX substantially raised basal tone to a greater degree in endothelium-intact preparations than in endothelium-denuded preparations. These results indicate that EDHF may exert its relaxing action through intermediate conductance Ca2+- ***activated*** and ***voltage*** -dependent ***K*** + ***channels*** in canine coronary arteries. In addition, EDHF may play a role in maintaining basal vascular tone.

L7 ANSWER 2 OF 4283 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:231734 BIOSIS
DN PREV199800231734
TI Arachidonic acid inhibits norepinephrine release through blocking of ***voltage*** -sensitive Ca2+ channels in PC12 cells.
AU Choi, Se-Young; Park, Tae-Ju; Choi, Jun-Ho; Kim, Kyong-Tai (1)
CS (1) Dep. Life Science, Basic Science Res. Inst., Pohang Univ. Science Technology, Pohang 790-784 South Korea
SO Korean Journal of Biological Sciences, (***March, 1997***) Vol. 1, No. 1, pp. 81-86.
ISSN: 1226-5071.
DT Article
LA English
AB We studied the mechanism of arachidonic acid on the secretion of a neurotransmitter in rat pheochromocytoma PC12 cells. Arachidonic acid inhibited the 70 mM K+-induced secretion of norepinephrine. Arachidonic acid also inhibited the 70 mM K+-induced Ca2+ mobilization which is due to the opening of the ***voltage*** -sensitive Ca2+ channels (VSCC). Both the half maximal inhibitory concentration (IC50) of the norepinephrine secretion and VSCC coincided at 30 muM. The major oxidized metabolites of arachidonic acid, prostaglandins did not mimic the inhibitory effect of arachidonic acid. Nordihydroguaiaretic acid (NDGA) and indomethacin which are inhibitors of lipoxygenase and cyclooxygenase, respectively, did not block the inhibitory effect of arachidonic acid. The results suggest that arachidonic acid serves as a signal itself, not in the form of metabolites. The pretreatment of various ***K*** + ***channel*** ***blockers*** such as 4-aminopyridine, tetraethylammonium, glipizide, or glibenclamide also did not show any effect on the inhibitory effect of arachidonic acid. Through these results we suggest that arachidonic acid regulates VSCC directly and affects the secretion of neurotransmitters.

L7 ANSWER 3 OF 4283 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:224504 BIOSIS
DN PREV199800224504
TI Experimental study on alteration of membrane ionic currents in pulmonary arterial myocytes from monocrotaline-induced pulmonary hypertensive rat.
AU Muraki, Satoshi; Tohse, Noritsugu
CS First Dep. Physiol., Sapporo Med. Univ. Sch. Med., S1 W17 Chuo-ku, Sapporo 060 Japan
SO Sapporo Medical Journal, (***Oct., 1997***) Vol. 66, No. 5, pp. 201-213.
ISSN: 0036-472X.
DT Article
LA Japanese
SL Japanese; English
AB Pulmonary hypertension (PH) caused by an idiopathic process or various cardiopulmonary disorders is well known to be a fatal disease which is correlated with increased patient mortality. Despite its severity and difficulties in treatment or management, the physiological basis of PH has not been understood completely. The present study was undertaken to examine the changes in ionic currents of pulmonary artery smooth muscle cell (PASMC), under the pathological condition of PH. As an animal model of PH, monocrotaline-induced pulmonary hypertensive rats were produced by single subcutaneous injection of 60 mg/kg monocrotaline (MCT). To confirm that PH developed successfully on the experimental days (18-21 days) after the treatment with MCT, right ventricular systolic pressure was measured as a indicator of pulmonary artery pressure. The whole cell patch clamp method was applied to single PASMC freshly isolated from the main pulmonary artery along with some intrapulmonary branches of MCT injected rats (MCT rats) and saline injected control rats (Saline rats). Resting membrane potential of PASMC was not different between the two groups in the current-clamp mode. Outward currents elicited by depolarizing test pulse from a holding potential of -43 mV were remarkably smaller in MCT rats than in Saline rats, using patch pipettes with 0.1 mM EGTA. On the other hand, when the pipette contained 10 mM EGTA, the outward currents were almost similar between the two groups. To identify the component responsible for the reduction of outward currents, the effect of inhibitors of K+ currents were examined. Nisoldipine (1 muM), which indirectly inhibits Ca2+- ***activated*** ***K*** + ***channel*** by blocking L-type Ca2+ channels, was less effective in MCT rats than in Saline rats. Tetraethylammonium (5 mM), selective Ca2+- ***activated*** ***K*** + ***channel*** inhibitor, was also less effective in MCT rats than in Saline rats. In contrast, 4-aminopyridine (4 mM), selective ***voltage*** gated K+ channel inhibitor, was almost equally effective on both. The current density of L-type Ca2+ channel current in MCT and Saline rats was also investigated using 1 muM nisoldipine. Ca2+ currents were small in MCT rats. Because elevation of cytoplasmic Ca2+ concentration of PASMC is expected under the pathological condition of PH, all these results suggest that elevation of cytoplasmic Cal+ leads to a reduction of Ca2+-activated K+ currents and Ca2+ currents in PASMC.

L7 ANSWER 4 OF 4283 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:97269 BIOSIS
DN PREV199800097269
TI Inhibition of dendritic calcium influx by activation of G-protein-coupled receptors in the hippocampus.

AU Chen, Huanmian (1); Lambert, Nevin A. (1)
CS (1) Dep. Pharmacol. Toxicol., Medical Coll. Georgia, Augusta, GA 30912-2300 USA
SO Journal of Neurophysiology (Bethesda), (***Dec., 1997***) Vol. 78, No. 6, pp. 3484-3488.
ISSN: 0022-3077.
DT Article
LA English
AB Gi proteins inhibit ***voltage*** -gated calcium channels and ***activate*** inwardly rectifying ***K*** + ***channels*** in hippocampal pyramidal neurons. The effect of activation of G-protein-coupled receptors on action potential-evoked calcium influx was examined in pyramidal neuron dendrites with optical and extracellular ***voltage*** recording. We tested the hypotheses that 1) activation of these receptors would inhibit calcium channels in dendrites; 2) hyperpolarization resulting from ***K*** + ***channel*** ***activation*** would deinactivate low-threshold, T-type calcium channels on dendrites, increasing calcium influx mediated by these channels; and 3) activation of these receptors would inhibit propagation of action potentials into dendrites, and thus indirectly decrease calcium influx. Activation of adenosine receptors, which couple to Gi proteins, inhibited calcium influx in cell bodies and proximal dendrites without inhibiting action-potential propagation into the proximal dendrites. Inhibition of dendritic calcium influx was not changed in the presence of 50 muM nickel, which preferentially blocks T-type channels, suggesting influx through these channels is not increased by activation of G-proteins. Adenosine inhibited propagation of action potentials into the distal branches of pyramidal neuron dendrites, leading to a three- to fourfold greater inhibition of calcium influx in the distal dendrites than in the soma or proximal dendrites. These results suggest that ***voltage*** -gated calcium channels are inhibited in pyramidal neuron dendrites, as they are in cell bodies and terminals and that G-protein-mediated inhibition of action-potential propagation can contribute substantially to inhibition of dendritic calcium influx.

L7 ANSWER 5 OF 4283 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:97261 BIOSIS
DN PREV199800097261
TI Modulation of multiple potassium currents by metabotropic glutamate receptors in neurons of the hypothalamic supraoptic nucleus.
AU Schrader, L. A.; Tasker, J. G. (1)
CS (1) Neurosci. Training Program, Tulane Univ., New Orleans, LA 70118 USA
SO Journal of Neurophysiology (Bethesda), (***Dec., 1997***) Vol. 78, No. 6, pp. 3428-3437.
ISSN: 0022-3077.
DT Article
LA English
AB We studied the effects of activation of the metabotropic glutamate receptors on intrinsic currents of magnocellular neurons of the supraoptic nucleus (SON) with whole cell patch-clamp and conventional intracellular recordings in coronal slices (400 mum) of the rat hypothalamus. Trans-(+-)-1-amino-1,3-cyclopentane dicarboxylic acid (trans-ACPD, 10-100 muM), a broad-spectrum metabotropic glutamate receptor agonist, evoked an inward current (18.7 +- 3.45 pA) or a slow depolarization (7.35 +- 4.73 mV) and a 10-30% decrease in whole cell conductance in apprx 50% of the magnocellular neurons recorded at resting membrane potential. The decrease in conductance and the inward current were caused largely by the attenuation of a resting potassium conductance because they were reduced by the replacement of intracellular potassium with an equimolar concentration of cesium or by the addition of ***potassium*** ***channel*** ***blockers*** to the extracellular medium. In some cells, trans-ACPD still elicited a small inward current after blockade of potassium currents, which was abolished by the calcium channel blocker, CdCl2. Trans-ACPD also reduced ***voltage*** -gated and Ca2+-activated K+ currents in these cells. Trans-ACPD reduced the transient outward current (IA) by 20-70% and/ or the IA-mediated delay to spike generation in apprx 60% of magnocellular neurons tested. The cells that showed a reduction of IA generally also showed a 20-60% reduction in a ***voltage*** -gated, sustained outward current. Finally, trans-ACPD attenuated the Ca2+-dependent outward current responsible for the afterhyperpolarization (IAHP) in apprx 60% of cells tested. This often revealed an underlying inward current thought to be responsible for the depolarizing afterpotential seen in some magnocellular neurons. (RS)-3,5-dihydroxyphenylglycine, a group I receptor-selective agonist, mimicked the effects of trans-ACPD on the resting and ***voltage*** -gated K+ currents. (RS)-alpha-methyl-4-carboxyphenylglycine, a group I/II metabotropic glutamate receptor antagonist, blocked these effects. A group II receptor agonist, 2S,1'S,2'S-2 carboxycyclopropylglycine and a group III receptor agonist, L(+)-2-amino-4-phosphonobutyric acid, had no effect on the resting or ***voltage*** -gated K+ currents, indicating that the reduction of K+ currents was mediated by group I receptors. About 80% of the SON cells that were labeled immunohistochemically for vasopressin responded to metabotropic glutamate receptor activation, whereas only 33% of labeled oxytocin cells responded, suggesting that metabotropic receptors are expressed preferentially in vasopressinergic neurons. These data indicate that activation of the group I metabotropic glutamate receptors leads to an increase in the postsynaptic excitability of magnocellular neurons by blocking resting K+ currents as well as by reducing ***voltage*** -gated and Ca2+-activated K+ currents.

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L2 2176141 S BLOCKER? OR ACTIVAT?
L3 68771 S POTASSIUM CHANNEL? OR K CHANNEL?
L4 21927 S L3 (3A) L2
L5 0 S L4 AND DRUG SREEN?
L6 14252 S L4 AND PY<1998
L7 4283 S L6 AND VOLTAGE
L8 2055401 S ACTIVAT?

=> s l3 (3a) l2
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=> s l11 and voltage
L12 3180 L11 AND VOLTAGE

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L12 ANSWER 1 OF 3180 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:507129 BIOSIS
DN PREV199800507129
TI Role of K+ channels in EDHF-dependent relaxation induced by acetylcholine in canine coronary artery.
AU Nakashima, Yoshihito; Toko, Yukio; Fukami, Yasumasa; Hibino, Michitaka; Okumura, Kenji; Ito, Takayuki (1)
CS (1) Intern. Med. 2, Nagoya Univ. Sch. Med., 65 Turumai-cho, Showa-ku, Nagoya 466 Japan
SO Heart and Vessels, (1997) Vol. 12, No. 6, pp. 287-293.
ISSN: 0910-8327.
DT Article
LA English
AB To identify the K+ channels responsible for endothelium-derived hyperpolarizing factor (EDHF)-dependent relaxation, we studied the effects of various K+ channel blockers on acetylcholine-induced relaxation, which persists even in the presence of both an inhibitor of nitric oxide synthase and that of cyclooxygenase, in canine coronary artery rings. A nonselective K+ channel blocker, tetrabutylammonium (TBA), a large and intermediate conductance Ca2+- ***activated*** ***K*** + ***channel*** blocker, charybdotoxin (CTX), and a ***voltage*** -dependent K+ channel blocker, 4-aminopyridine (4-AP), significantly inhibited this residual relaxation. A combined treatment with CTX and 4-AP almost completely blocked the relaxation. Neither a large (iberiotoxin) nor a small (apamin) conductance Ca2+- ***activated*** ***K*** + ***channel*** blocker blocked the relaxation. We also investigated effects of K+ channel blockers on basal tone to determine whether or not EDHF is involved in regulating basal tone. TBA and CTX substantially raised basal tone to a greater degree in endothelium-intact preparations than in endothelium-denuded preparations. These results indicate that EDHF may exert its relaxing action through intermediate conductance Ca2+- ***activated*** and ***voltage*** -dependent ***K*** + ***channels*** in canine coronary arteries. In addition, EDHF may play a role in maintaining basal vascular tone.

L12 ANSWER 2 OF 3180 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:224504 BIOSIS
DN PREV199800224504
TI Experimental study on alteration of membrane ionic currents in pulmonary arterial myocytes from monocrotaline-induced pulmonary hypertensive rat.
AU Muraki, Satoshi; Tohse, Noritsugu
CS First Dep. Physiol., Sapporo Med. Univ. Sch. Med., S1 W17 Chuo-ku, Sapporo 060 Japan
SO Sapporo Medical Journal, (***Oct., 1997***) Vol. 66, No. 5, pp. 201-213.
ISSN: 0036-472X.
DT Article
LA Japanese
SL Japanese; English
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the treatment with MCT, right ventricular systolic pressure was measured as a indicator of pulmonary artery pressure. The whole cell patch clamp method was applied to single PASMC freshly isolated from the main pulmonary artery along with some intrapulmonary branches of MCT injected rats (MCT rats) and saline injected control rats (Saline rats). Resting membrane potential of PASMC was not different between the two groups in the current-clamp mode. Outward currents elicited by depolarizing test pulse from a holding potential of -43 mV were remarkably smaller in MCT rats than in Saline rats, using patch pipettes with 0.1 mM EGTA. On the other hand, when the pipette contained 10 mM EGTA, the outward currents were almost similar between the two groups. To identify the component responsible for the reduction of outward currents, the effect of inhibitors of K+ currents were examined. Nisoldipine (1 muM), which indirectly inhibits Ca2+- ***activated*** ***K*** + ***channel*** by blocking L-type Ca2+ channels, was less effective in MCT rats than in Saline rats. Tetraethylammonium (5 mM), selective Ca2+- ***activated*** ***K*** + ***channel*** inhibitor, was also less effective in MCT rats than in Saline rats. In contrast, 4-aminopyridine (4 mM), selective ***voltage*** gated K+ channel inhibitor, was almost equally effective on both. The current density of L-type Ca2+ channel current in MCT and Saline rats was also investigated using 1 muM nisoldipine. Ca2+ currents were small in MCT rats. Because elevation of cytoplasmic Ca2+ concentration of PASMC is expected under the pathological condition of PH, all these results suggest that elevation of cytoplasmic Cal+ leads to a reduction of Ca2+-activated K+ currents and Ca2+ currents in PASMC.

L12 ANSWER 3 OF 3180 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:97269 BIOSIS
DN PREV199800097269
TI Inhibition of dendritic calcium influx by activation of G-protein-coupled receptors in the hippocampus.
AU Chen, Huanmian (1); Lambert, Nevin A. (1)
CS (1) Dep. Pharmacol. Toxicol., Medical Coll. Georgia, Augusta, GA 30912-2300 USA
SO Journal of Neurophysiology (Bethesda), (***Dec., 1997***) Vol. 78, No. 6, pp. 3484-3488.
ISSN: 0022-3077.
DT Article
LA English
AB Gi proteins inhibit ***voltage*** -gated calcium channels and ***activate*** inwardly rectifying ***K*** + ***channels*** in hippocampal pyramidal neurons. The effect of activation of G-protein-coupled receptors on action potential-evoked calcium influx was examined in pyramidal neuron dendrites with optical and extracellular ***voltage*** recording. We tested the hypotheses that 1) activation of these receptors would inhibit calcium channels in dendrites; 2) hyperpolarization resulting from ***K*** + ***channel*** ***activation*** would deinactivate low-threshold, T-type calcium channels on dendrites, increasing calcium influx mediated by these channels; and 3) activation of these receptors would inhibit propagation of action potentials into dendrites, and thus indirectly decrease calcium influx. Activation of adenosine receptors, which couple to Gi proteins, inhibited calcium influx in cell bodies and proximal dendrites without inhibiting action-potential propagation into the proximal dendrites. Inhibition of dendritic calcium influx was not changed in the presence of 50 muM nickel, which preferentially blocks T-type channels, suggesting influx through these channels is not increased by activation of G-proteins. Adenosine inhibited propagation of action potentials into the distal branches of pyramidal neuron dendrites, leading to a three- to fourfold greater inhibition of calcium influx in the distal dendrites than in the soma or proximal dendrites. These results suggest that ***voltage*** -gated calcium channels are inhibited in pyramidal neuron dendrites, as they are in cell bodies and terminals and that G-protein-mediated inhibition of action-potential propagation can contribute substantially to inhibition of dendritic calcium influx.

L12 ANSWER 4 OF 3180 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:97051 BIOSIS
DN PREV199800097051
TI Pathway-specific effects of calcitonin gene-related peptide on irideal arterioles of the rat.
AU Hill, C. E. (1); Gould, D. J.
CS (1) Div. Neuroscience, John Curtin Sch. Med. Res., Australian National Univ., Canberra, ACT 2601 Australia
SO Journal of Physiology (Cambridge), (***Dec. 15, 1997***) Vol. 505, No. 3, pp. 797-809.
ISSN: 0022-3751.
DT Article
LA English
AB 1. Arteriolar diameter and membrane ***voltage*** have been measured to investigate the actions of calcitonin gene-related peptide (CGRP) in rat irideal arterioles. 2. Activation of sensory nerves inhibited sympathetic vasoconstriction, reduced the accompanying 40-50 mV depolarization by 90% and caused a 4 mV hyperpolarization. 3. The inhibition of vasoconstriction was prevented by either preincubation in L-NAME (10 muM), to inhibit nitric oxide production, by preincubation in the cell-permeant adenylate cyclase inhibitor dideoxyadenosine (1 mM) or by preincubation in the ATP-sensitive potassium channel blocker glibenclamide (10 muM). The subsequent addition of a nitric oxide donor to the glibenclamide solution inhibited nerve-mediated vasoconstriction, suggesting that the potassium channel involvement preceded the production of nitric oxide. The small hyperpolarization was not affected by L-NAME. 4. Nerve-mediated vasodilatation persisted in the presence of L-NAME (10 muM) but was abolished with the CGRP1 receptor antagonist CGRP8-37. 5. In arterioles preconstricted with the alpha2-adrenoceptor agonist UK-14304 (100 nM), exogenous CGRP caused a hyperpolarization and a dose-dependent vasodilatation, neither of which was affected by L-NAME (10 muM). 6. In arterioles preconstricted with 30 mM KCl, CGRP (10 nM) caused vasodilatation but not hyperpolarization, suggesting that the hyperpolarization was not causal to the vasodilatation. 7. Forskolin (30 nM), in the presence of L-NAME to prevent effects due to nitric oxide, caused vasodilatation. 8. These results suggest that CGRP inhibits sympathetic nerve-mediated vasoconstriction through sequential increases in cyclic AMP and nitric oxide, while vasodilatation results from increases in cyclic AMP alone. The production of nitric oxide, but not its mechanism of action, appears to be dependent on the ***activation*** of ATP-sensitive ***potassium*** ***channels*** . The possible sites of action of these two pathways are discussed.

L12 ANSWER 5 OF 3180 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:94366 BIOSIS
DN PREV199800094366
TI K+ transport and capacitance of the basolateral membrane of the larval frog skin.
AU Hillyard, Stanley D. (1); Cantiello, Horacio F.; Van Driessche, Willy
CS (1) Dep. Biol. Sci., Univ. Nevada, 4505 Maryland Parkway, Las Vegas, NV 89154-4004 USA
SO American Journal of Physiology, (***Dec., 1997***) Vol. 273, No. 6 PART 1, pp. C1995-C2001.
ISSN: 0002-9513.
DT Article
LA English
AB Skin from larval bullfrogs was mounted in an Ussing-type chamber in which the apical surface was bathed with a Ringer solution containing 115 mM K+ and the basolateral surface was bathed with a Ringer solution containing 115 mM Na+. Ion transport was measured as the short-circuit current (Isc) with a low-noise ***voltage*** clamp, and skin resistance (Rm) was measured by applying a direct current ***voltage*** pulse. Membrane impedance was calculated by applying a ***voltage*** signal consisting of 53 sine waves to the command stage of the ***voltage*** clamp. From the ratio of the Fourier-transformed ***voltage*** and current signals, it was possible to calculate the resistance and capacitance of the apical and basolateral membranes of the epithelium (Ra and Rb, Ca and Cb, respectively). With SO42- as the anion, Rm decreased rapidly within 5 min following the addition of 150 U/ml nystatin to the apical solution, whereas Isc increased from 0.66 to 52.03 muA/cm2 over a 60-min period. These results indicate that nystatin becomes rapidly incorporated into the apical membrane and that the increase in basolateral K+ permeability requires a more prolonged time course. Intermediate levels of Isc were obtained by adding 50, 100, and 150 U/ml nystatin to the apical solution. This produced a progressive decrease in Ra and Rb while Ca and Cb remained constant. With Cl- as the anion, Isc values increased from 2.03 to 89.57 muA/cm2 following treatment with 150 U/ml nystatin, whereas with gluconate as the anion Isc was only increased from 0.63 to 11.64 muA/cm2. This suggests that the increase in basolateral K+ permeability produced by nystatin treatment, in the presence of more permeable anions, is due to swelling of the epithelial cells of the tissue rather than the gradient for apical K+ entry. Finally, Cb was not different among skins exposed to Cl-, SO42-, or gluconate, despite the large differences in Isc, nor did inhibition of Isc by treatment with hyperosmotic dextrose cause significant changes in Cb. These results support the hypothesis that increases in cell volume ***activate*** ***K*** + ***channels*** that are already present in the basolateral membrane of epithelial cells.

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FULL ESTIMATED COST		59.73	59.94

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